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THE UNITED STATES OF AMERICA

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United States Patent and Trademark Office

October 23, 2003

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APPLICATION NUMBER: *60/400,038*
FILING DATE: *August 02, 2002*
RELATED PCT APPLICATION NUMBER: *PCT/US03/24188*

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

M. Sias

M. SIAS
Certifying Officer

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PTO/SB/16 (10-01)
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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No.

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Khaled F.	Mansour	Detroit, MI

☑ *Additional inventors are being named on the* 1 *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

Method to Determine A Mathematical Flow Limitation and Upper Airway Resistance

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

☐ Customer Number ______ *Type Customer Number here* → *Place Customer Number Bar Code Label here*

OR

☑ Firm or Individual Name	Department of Veterans Affairs				
Address	Office of the General Counsel (024M)				
Address	810 Vermont Avenue, NW				
City	Washington	State	DC	ZIP	20420
Country	USA	Telephone	(202) 273-6384	Fax	(202) 273-6388

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 71 ☐ CD(s), Number

☑ Drawing(s) *Number of Sheets* ☐ Other (specify)

☐ Application Data Sheet. See 37 CFR 1.76

METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT

☐ Applicant claims small entity status. See 37 CFR 1.27.

☐ A check or money order is enclosed to cover the filing fees

☐ The Commissioner is hereby authorized to charge filing fees or credit any overpayment to Deposit Account Number:

☑ Payment by credit card. Form PTO-2038 is attached.

FILING FEE AMOUNT ($): $160.00

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☐ No.

☑ Yes, the name of the U.S. Government agency and the Government contract number are. U.S. Department of Veterans Affairs

Respectfully submitted,

SIGNATURE Michael J. Gonet

Date 08/01/2002

TYPED or PRINTED NAME Michael J. Gonet

REGISTRATION NO. *(if appropriate)* 31465

TELEPHONE (202) 273-8137

Docket Number: VA 02-102

USE ONLY FOR FILING A PROVISIONAL APPLICATION FOR PATENT

This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C. 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C. 20231.

08/02/02
JC923 U.S. PTO
60/400038

PROVISIONAL APPLICATION COVER SHEET
Additional Page

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Docket Number	VA 02-102

INVENTOR(S)/APPLICANT(S)

Given Name (first and middle [if any])	Family or Surname	Residence (City and either State or Foreign Country)
James	Rowley	Detroit, MI
Mahdi	Shkoukani	Detroit, MI
M. Safwan	Badr	Detroit, MI

Number 2 of 2

WARNING: Information on this form may become public. Credit card information should not be included on this form. Provide credit card information and authorization on PTO-2038.

DEPARTMENT OF VETERANS AFFAIRS
Medical Center
4646 John R
Detroit, Michigan 48201

July 15, 2002

In Reply Refer To: 11R

Director
Technology Transfer Program (122IT)
Department of Veterans Affairs
1400 I Street, NW
Suite 700
Washington, DC 20005

Dear Sir:

I am in full support of the attached invention disclosure entitled "Method to Determine a Mathematical Flow Limitation and Upper Airway Resistance", which is submitted for your consideration.

Dr. Michael Samson, Chief of Staff, Dr. Mark Edelstein, ACOS for Medicine and Dr. Richard E. Miller, ACOS for R&D at this facility are in concurrence with this invention disclosure.

If further information is needed, please contact Richard E. Miller, M.D., ACOS/R&D, at (313) 576-3430.

Sincerely yours,

for Michael K. Wheeler
Director

Department Of Veterans Affairs Headquarters
Washington, D.C. 20420
Reporting Invention

1. Title of Invention: Method to Determine A Mathematical Flow Limitation and Upper Airway Resistance

2. Name of inventor and each co-inventor, business address, phone number (include area code), fax number, email and official title or position.

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Detroit. Mi 48202
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Fax: (313) 576-1377
E-Mail: kmansour@intmed.wayne.edu
Without-compensation Research Associate

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E-Mail: jrowley@intmed.wayne.edu
Fee Basis/Consultant physician (VA)
Assistant Professor and Director of Hutzel Sleep Lab.

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Physician (.6) and Principle Investigator (VA)
Professor and Division Chief. Pulmonary, Critical Care and Sleep Medicine
Harper Hospital
3990 John R, 3 Hudson
Detroit, MI 48201
Phone: (313) 745-6033

3. Brief statement describing each inventor and co-inventor's research duties and responsibilities for the VA at the time the invention was made. If none, please explain. Further, how did such duties and responsibilities contribute or relate to the invention. If non-VA, please identify as such.

Khaled Mansour: This is part of his Ph.D. dissertation and a research project in upper airway mechanics. He has contributed to the theory, data analysis, and design method for an experimental application of the data. Since the data analyses were in agreement with the theory, he designed two different codes using visual basic software. One of the codes is used to calculate the upper airway resistance and the other is to detect inspiratory flow limitation of the breaths. These codes (programs) were created as an alternative metric to handle large data acquisition and to speed the process in automatic and reproducible fashion.

James Rowley: Dr. Rowley served as assistant supervisor of the project, providing ideas and corrections, planning the work, performing statistical measurement, and providing oversight for the whole project.

Mahdi Shkoukani: He provided experimental data acquisition and processing, input to the methods and theory of the project and software, data analysis, code validation and final results validation.

M.Safwan Badr: Dr. Badr is Chief Supervisor/decision maker. He provided theory correction and validation and planned, organized and refined the work.

a. Please attach a copy of a position description (PD) for each VA inventor.

Two of the co-inventors are MDs who do not have position descriptions and both without-compensation employees do not have official position descriptions.

b. If the inventor holds a WOC (without compensation) appointment, please include a copy of the signed VA-WOC Appointee Intellectual Property Agreement. If none, please indicate whether or not the employee was paid on an IPA to the VA during the time the invention was being worked

Copies of VA-WOC agreements are attached. Neither WOC employee was or is on an IPA.

4. Name and address of the facility at which the invention was made:

John D. Dingell VA Medical Center
4646 John R
Detroit. MI 48201

5. Contribution of the VA to the invention in staff, funds (list amount), equipment, facilities, materials /or supplies

- Invention was made in Sleep Research Lab at the VA Medical Center, Room C-3436
- Computer equipments and software - $6,330 for 2 ½ years
- Scientific articles - $2000

6. Please list all other government contribution, such as NIH grants

50% of the funds for the graduate student salary came from NIH grants.

7. Contribution of any non-government organizations, including a university or institution of higher learning, to the invention in staff, funds (list amount), equipment, facilities, materials/or supplies, time or services on official duty for such entity. (Please indicate the source, nature, and value of contribution).

- Wayne State University - Department of Medicine offered the grants for this invention.
- Salary for graduate students - 70,000 for 2 ½ years
- Computer equipments and software - $6.340 for 2 ½ years
- Text books and manuals $2000
- 1000 hours to develop and Design the code - 1000*($100/hr)= $100,000

8. Describe the invention completely, using the outline given below. Sketches, prints, photos, and any pertinent manuscript should be attached to this disclosure. Manuscripts generally following the outline are acceptable substitutes

a. General Purpose. State in general terms the purpose and object of the invention

The purpose of this work is to develop automated methods to measure two important indices of upper airway mechanics in an automated, objective and reproducible manner.

1. Upper airway resistance
2. Inspiratory flow limitation.

b. Background. Describe the prior art (identify by patent number or journal citation, if possible) and indicate how the invention differs and is more advantageous than prior art.

The ability to detect inspiratory flow limitation objectively may have significant relevance to the diagnosis of sleep-disordered breathing (SDB). The description of the upper airway

resistance syndrome (UARS) expanded the spectrum of SDB by including patients without episodes of apnea or identifiable hypopnea. Detection of inspiratory flow limitation is critical to the diagnosis of UARS. Unfortunately, detection of inspiratory flow limitation was based on subjective visual detection of a square flow profile without pressure measurements. Likewise, manual analysis of the pressure-flow loop is laborious and fraught with subjective pitfalls.

We have developed a novel method based on engineering theory to detect inspiratory flow limitation and compute upper airway resistance. This method can be applied in an automated manner to a large amount of data just in 1 minute for 50 breaths. Using conventional methods, this analysis consumed more than 5 hours of time from experienced laboratory personnel and was fraught with subjective pitfalls, especially in the determination of inspiratory flow limitation. Thus, our method can be used on a large number of breaths in an automated fashion and may be useful in future studies that assess the Sleep Disordered Breathing.

Several mathematical models have been proposed to characterize the pressure flow relationship in the pharyngeal upper airway; however these models did not develop to specify inspiratory flow limitation or resistance in an objective, automated and reproducible method.

i) Rohrer. F. The resistance in the Human airway. Pfluegers arch physiol 162:255-299, Germany (1915)

ii) Hudgel. D, Hendricks C, and Hamilton H. Characteristics of the upper airway pressure- flow relationship during sleep. J Applied physiology. 64 (5); 1930-1935 (1988)

iii) Guilleminault, C., R. Stoohs, T. Shiomi, C. Kushida, and I. Schnittger. Upper airway resistance syndrome, nocturnal blood pressure monitoring, and borderline hypertension. *Chest* 109: 901-908, 1996.

iv) Hosselet, J., I. Ayappa, R. G. Norman, A. C. Krieger, and D. M. Rapoport. Classification of sleep-disordered breathing. *Am J Respir Crit Care Med* 163: 398-405, 2001.

c. Description and Operation. Describe completely (sufficient to permit the preparation of a patent application), the construction of the invention using reference characters to identify components in attached illustrations. Give a description of one complete operational cycle. If the invention relates to the synthesis or identification of a new composition of matter, describe the product in a structured form, if possible, and the process of making it. Include all available information regarding its physical characteristics and all test data evidencing its utility

First we get the raw data of pressure – flow from the subject. Inspiratory air flow was measured by a heated pneumotachometer (model 3700A, Hans Rudolph, Kansas City, MO). Supraglottic pressure was measured by using a transducer-tipped pressure catheter (model TC-500XG, Millar instruments, Houston, TX). Data for both signals were recorded on an acquisition program (Power Lab on Mac OS, version 4.0, Grand Junction, Colorado). Then, raw data was exported to an Excel spread sheet. (See Fig 1A which represents extraction of the breath from the polygraph, as indicated on box label; others represent various channels.) At this point, our program is ready to do its action. The data in the spread sheet then will be divided into breaths based on the fact that each breath would start with Flow = 0 and that inspiration precedes expiration. Then, adjusted pressure would be added as a new column to make sure that the first coordinate of every breath would be (Pressure=0, Flow=0). Next, a fourth column would be added as the resistance where resistance = adjusted Pressure/ Flow. Then, a table would be created presenting the value of resistance at fixed flow (flow= 0.20 L/s) for every breath. Finally, an X-Y graph would be plotted for every breath where adjusted pressure in the x-axis and flow in the y-axis. (See attachment Macro 1.)

The second program (see attachment Macro 2) follows the same steps mentioned in the first program up to calculating the adjusted pressure step. Then, the raw pressure column would be deleted and a column of flow and another for adjusted pressure would remain. Next, a curve fitting of the inspiratory rising limb flow-pressure Fig 1B, and Fig 1C (Fig 1B represent the whole loop of the Breath or the actual data, Fig 1C represent the curve fit dotted line, and solid line is the actual data, Fig 1D represent slope of the fitted data, for example the slope here is positive it is IFL) relationship would be executed to get a mathematical polynomial function $F(P)= A P^3 + B P^2 + CP+ D$, where A, B, C, and D are the coefficients (constants). The software will calculate the coefficients (A, B, C, D), and calculate the derivative of the mathematical model see Fig 1D (which represents the slope).

$$\frac{dF}{dP} = 3AP^2 + 2BP + C$$

If the derivative at the maximum actual flow is zero or positive then the breath is inspiratory flow limited. Inspiratory flow limitation is defined as cessation of increase in flow with a continuous decrease in pressure (becoming more negative) see Fig 1D, and Fig 3 (right panel, top right is the fitted function (gray line), and bottom right panel is the slope as it is shown positive slope)

$$\frac{dF}{dP} \geq 0 \longrightarrow \text{IFL}$$

If the derivative of the model at maximum actual is less than zero, it is non inspiratory flow limited, Fig 3 (Left panel, top represent curve fit for NIFl (gray line), bottom negative slope NIFL)

$$\frac{dF}{dP} < 0 \longrightarrow \text{NIFL}$$

Then we will calculate resistance by taking the reciprocal of the Coefficient C, as shown in Fig (2) (tangent solid line represent the linear portion where we should calculate the slope for the actual pressure flow loop)

$$\text{Re}\,sis\,\tan ce = \frac{1}{C}$$

The out put of the program consist of two Excel sheets as follows:

a. One sheet has a table for each breath. In the table there are a list for the Coefficients (A, B, C, D), and a column for breath type (NIFL, IFL), and resistance for each breath (Macro 2).

b. Second sheet shows the calculation of the Coefficients (A, B, C, D) on the Excel to get the curve fit, and calculation of the derivatives to get breath type, and resistance. In the same sheet we will get the chart for pressure flow loop of the actual data, and on the top of the graph we will get a duplicate curve for our model. On the same sheet we will get the derivative graph if it is positive, zero, or negative. (Macro 2)

d. Non-Technical Description. Describe on one page or less (double-spaced) the invention in terms understandable to non-scientists.

We developed two different programs. One program is to measure the upper airway resistance using the formula: <u>Resistance = Pressure/ Flow.</u>

Raw data of flow and pressure is exported to an excel spreadsheet. The program would then divide the data into individual breaths and adjust the pressure for every breath to make sure that both flow and pressure starts with the value 0. Next, each breath is graphed where Flow in the y-axis and pressure in the x-axis. Then, the slope between the points Flow =O and Flow=0.20 is calculated. The resistance would be then the inverse of the slope.

The second program does two functions. First, determine whether a breath is flow limited or not. Flow limitation is defined as cessation of increase in inspiratory flow with continuous decrease in pressure. The other function is to measure the upper airway resistance using the coefficient C which is obtained from the mathematical function that represents the Flow-Pressure curve for each breath ($F(P) = AP^3 + BP^2 + CP + D$) where Resistance = 1/C.

Using the flow and adjusted pressure data, the second program runs a curve fitting to describe the flow-pressure pressure in meaningful polynomial function ($F(P) = AP^3 + BP^2 + CP + D$). Then, the derivative of this function is calculated as follows: $F' = 3AP^2+2BP+C$
If the value of the derivative F' at maximum flow is equal or greater than zero then it is a flow limited breath, otherwise, it is a non flow limited breath. Finally, the program would measure the upper airway resistance using the equation: Resistance= 1/C.

9. Commercial possibilities, including quantity and sales price range, if available.

- This work has some commercial value for research and possibly clinical sleep laboratories. The program can be incorporated into current data acquisition packages in sleep labs and would allow for a rapid detection of inspiratory flow limitation. Automated scoring may save on personnel time and cost.

- We are expecting price range within $3000/ original copy; this will include technical support.

10. State any reasons for applying for a patent, or why publication would not be adequate to promote the availability of the invention to the public.

The unique features of our patent are:

- Theory and experimental results are tightly congruent. There is no model in the literature of upper airway mechanics, especially to detect inspiratory flow limitation accurately.
- This software allows for automated detection of inspiratory flow limitation and computation of resistance in the upper airway.
- As a special feature for this model we designed new codes and the code has ***special Algorithm*** that allows for rapid analysis of large quantities of data .

- The specific components of the algorithm are: Bring data points into array; normalize the moving flow and moving average, normalize the residual, identify noise and set it to continuous array.

- The code also provides a precise composite loop of several breathes (added on top of each other). These codes need to be copyrighted for public use and marketing.

11. State whether any other party or institution is interested in filing and administering a patent application on the invention.

Dual link between VA Medical Center and affiliate, Wayne State University, Detroit, Michigan. However, a CTAA has not yet been signed.

12. Publication or planned publication of description of the invention which would enable someone skilled in the technology to which the invention pertains to make and use the invention. If published, please include journal citation and attach a reprint, if available.

The invention has two parts – theory and software. The theory portion has been accepted (June 2002) by the Journal of Applied Physiology to be published in October or November of 2002. The software part of the invention has not yet been publicized.

13. State whether the invention has previously been disclosed, as for example, description and date of any sale or public use of the invention in the United States. Description should specify if the use was operational, or for testing purposes, and if there was any effort or intention to maintain the invention in secrecy after the operational use commenced.

No

14. Patent Application number, if already filed.

N/A

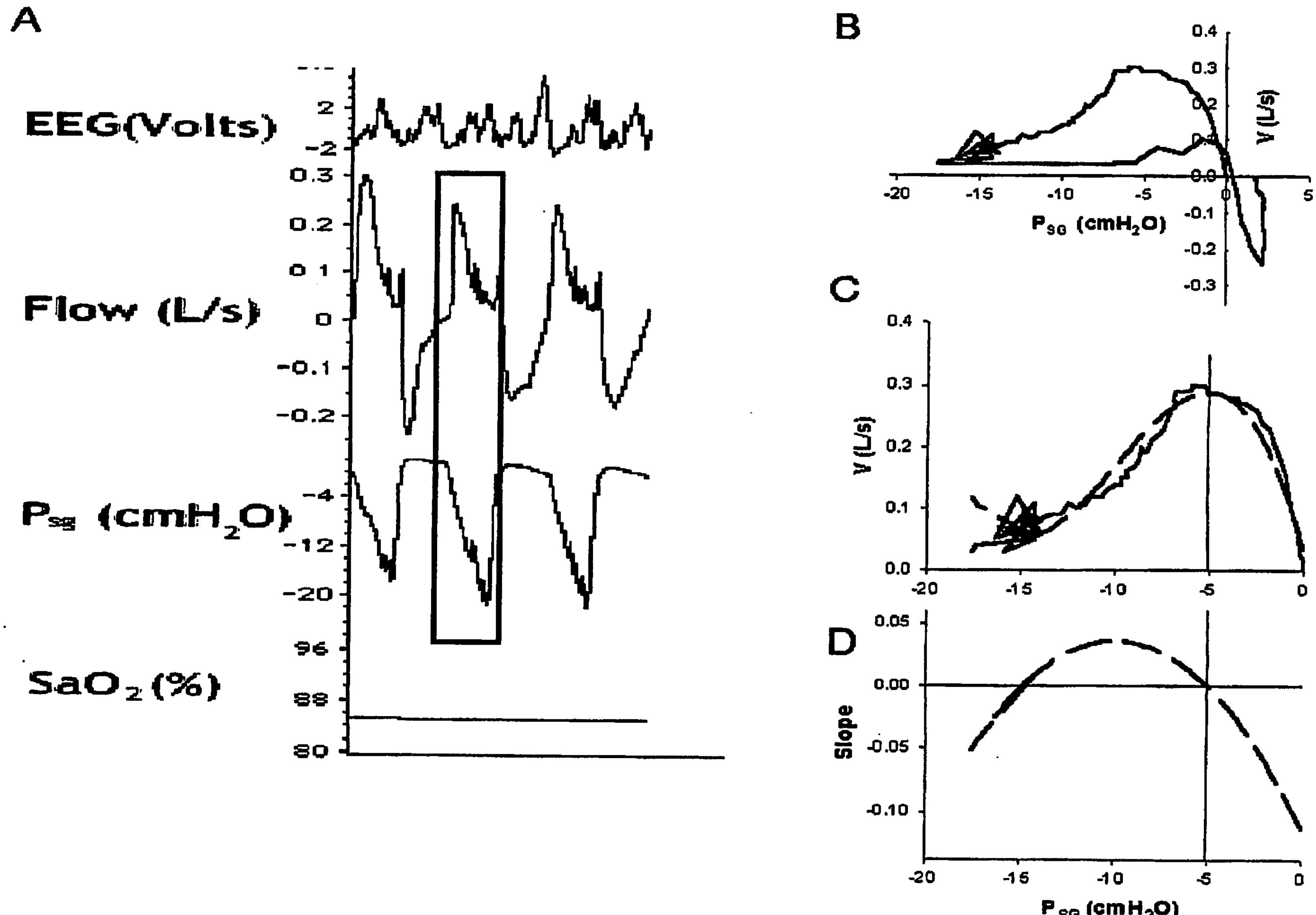
15. Signed certifications for each VA and WOC inventor that are listed are attached.

M.S. Badr, M.D.

Mahdi A. Shkoukani

Khaled Mansour, Ph.D.

James Rowley, M.D.



A
EEG(Volts)
Flow (L/s)
Psg (cmH2O)
SaO2 (%)
2
-2
0.3
0.2
0.1
0
-0.1
-0.2
-4
-12
-20
96
88
80
B
V (L/s)
PSG (cmH2O)
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-20
-15
-10
-5
0
5
C
V (L/s)
0.4
0.3
0.2
0.1
0.0
-20
-15
-10
-5
0
D
Slope
PSG (cmH2O)
0.05
0.00
-0.05
-0.10
-20
-15
-10
-5
0

Figure 1

Figure 2

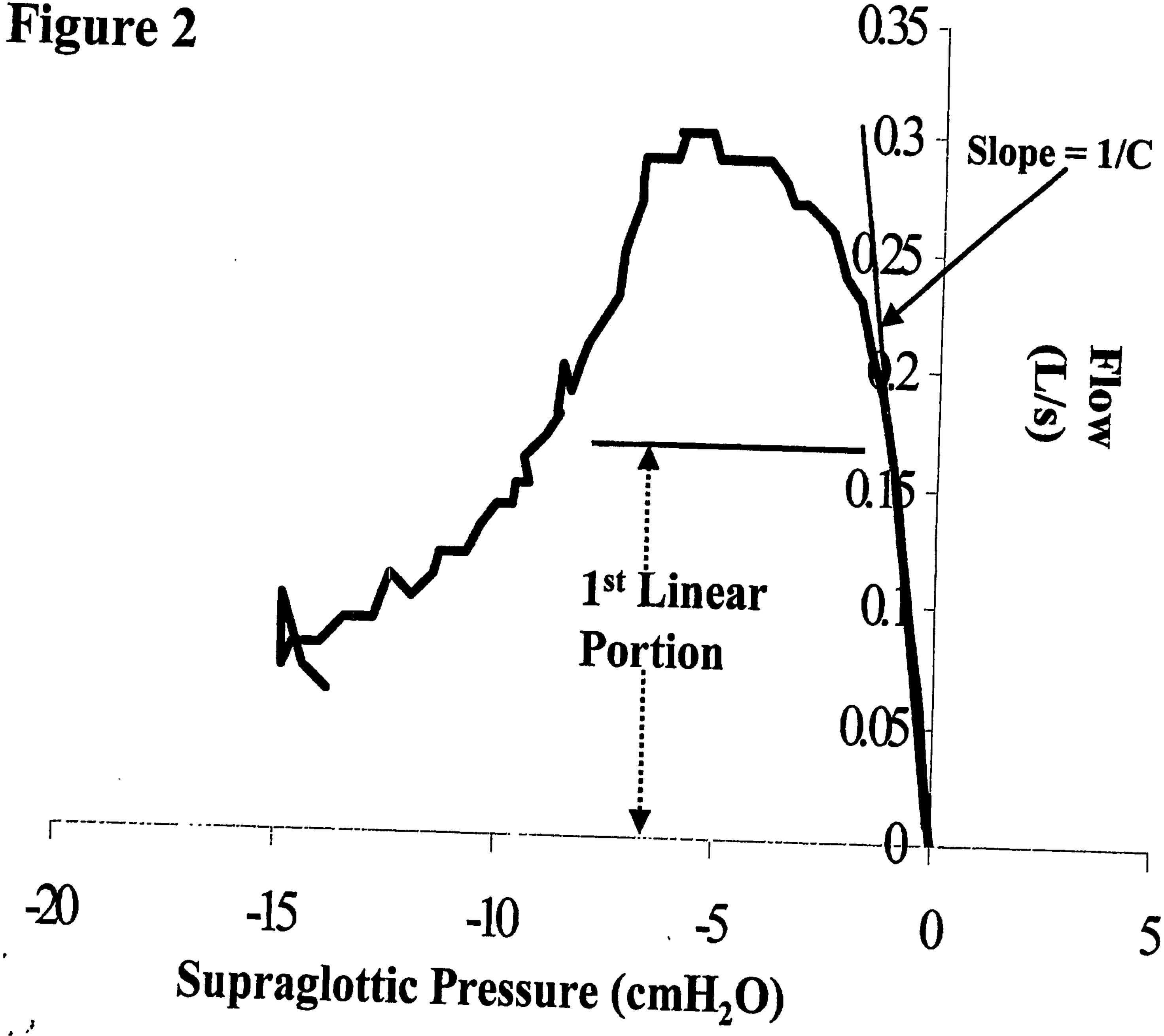


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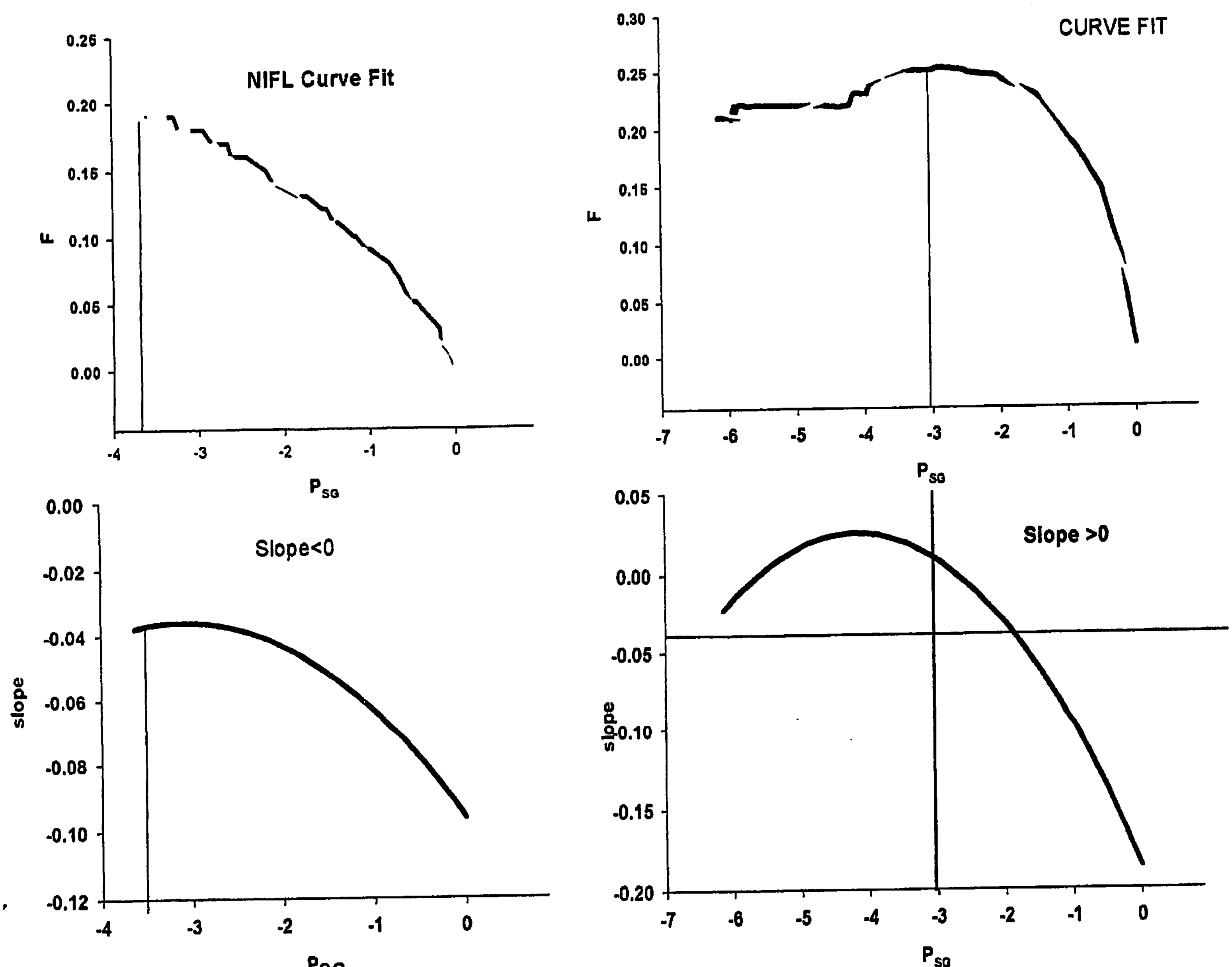
Figure 3


NIFL Curve Fit
F
0.25
0.20
0.15
0.10
0.05
0.00
-4
-3
-2
-1
0
P_{SG}
CURVE FIT
F
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-7
-6
-5
-4
-3
-2
-1
0
P_{SG}
Slope<0
slope
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
-0.12
-4
-3
-2
-1
0
P_{SG}
Slope >0
slope
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-7
-6
-5
-4
-3
-2
-1
0
P_{SG}

Example MACRO 1

Group 1	raw pressure		
flow	Pressure	adj. P	resistance
0.04	-5.87	-0.12	-2.85
0.08	-5.95	-0.20	-2.68
0.15	-6.25	-0.50	-3.41
0.16	-6.38	-0.63	-3.90
0.21	-6.76	-1.02	-4.91
0.22	-6.89	-1.15	-5.25
0.25	-7.36	-1.62	-6.42
0.26	-7.54	-1.79	-6.84
0.29	-8.03	-2.28	-7.95
0.30	-8.22	-2.47	-8.27
0.31	-8.68	-2.93	-9.32
0.32	-8.88	-3.13	-9.68
0.33	-9.47	-3.72	-11.33
0.32	-9.53	-3.79	-11.66
0.33	-9.63	-3.88	-11.87
0.33	-9.65	-3.90	-12.01
0.33	-9.77	-4.02	-12.05
0.33	-9.82	-4.08	-12.25
0.34	-9.98	-4.23	-12.34
0.35	-10.02	-4.27	-12.19
0.35	-10.14	-4.39	-12.66
0.35	-10.17	-4.42	-12.59
0.35	-10.23	-4.48	-12.64
0.35	-10.21	-4.47	-12.65

Adjusted

Group	FLOW	Pressure	Resistance
Group 1	0.21	-1.02	-4.91
Group 2	0.21	-1.11	-5.22
Group 3	0.21	-0.88	-4.11
Group 4	0.20	-1.10	-5.40
Group 5	0.20	-1.13	-5.54
Group 6	0.21	-1.10	-5.16
Group 7	0.22	-1.08	-4.86
Group 8	0.21	-1.29	-6.27
Group 9	0.21	-0.98	-4.62
Group 10	0.20	-1.14	-5.78
Group 11	0.20	-1.31	-6.40
Group 12	0.21	-1.50	-7.10
Group 13	0.20	-1.75	-8.60
Group 14	0.21	-1.94	-9.42
Group 15	0.20	-1.83	-9.38
Group 16	0.19	-2.27	-12.09

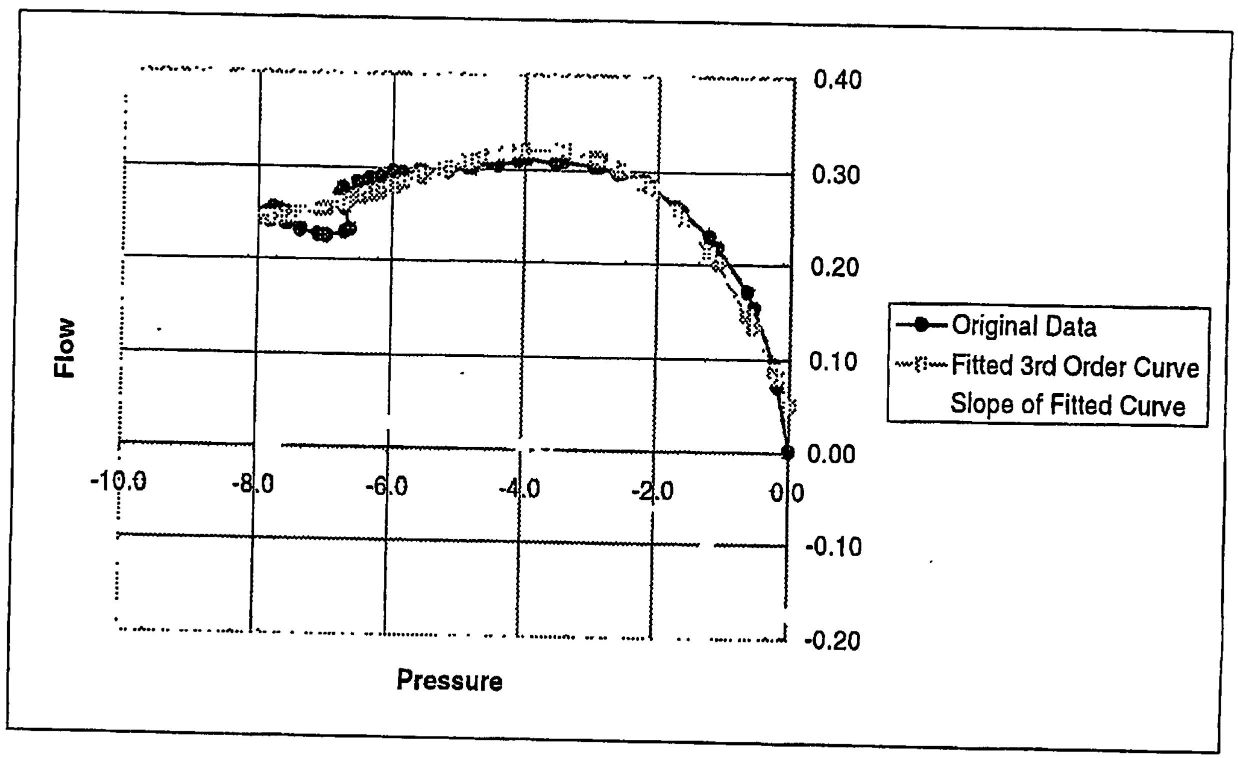
ress	Group	First Row	Last Row	pMax	pPMax
	b1	4	174	-7.91	-0.79

Resistance=-5

Coeff. A	Coeff. B	Coeff. C	Coeff D	Type	resis
-0.0019	-0.0030	-0.1728	-0.0040	FL	-5.0000
		0.1700			

Flow b1	adj press
0.00	0.00
0.07	-0.18
0.09	-0.24
0.15	-0.54
0.17	-0.64
0.22	-1.09
0.23	-1.22
0.26	-1.63
0.26	-1.74
0.28	-2.09
0.29	-2.21
0.30	-2.53
0.30	-2.61
0.30	-2.88
0.30	-2.97
0.31	-3.41
0.31	-3.54
0.31	-3.96
0.31	-4.10
0.30	-4.41
0.31	-4.54
0.30	-4.79
0.30	-4.88
0.30	-5.16
0.30	-5.23
0.30	-5.51
0.30	-5.59
0.29	-5.84
0.30	-5.98
0.29	-6.17

MACRO 2



60400038 .080202

604000375 .080202

VA-WOC APPOINTEE INTELLECTUAL PROPERTY AGREEMENT

This agreement is made between Mahdi A. Shkoukani and the Department of Veterans Affairs (VA) in consideration of my without compensation (WOC) appointment by the VA Medical Center, Detroit, Michigan (VAMC) and performing VA-Approved Research (as defined below) utilizing VA resources. This agreement is not intended to be executed by WOC appointees exclusively performing clinical services, attending services, or educational activities at the VAMC.

1. I hold a WOC appointment at the VAMC for the purpose of performing research projects, evaluated and approved by the VA Research and Development Committee (VA-Approved Research), at that VAMC.

2. By signing this agreement, I understand that, except as provided herein, I am adding no employment obligations to the VA beyond those created when I executed the WOC appointment.

3. I have read and understand the VHA Intellectual Property Handbook 1200.18 (attached) which provides guidance and instruction regarding Invention disclosures, patenting and the transfer of new scientific discoveries.

4. Notwithstanding that I am an employee or appointee at Wayne State University, I will disclose to VA any invention that I make while acting within my VA-WOC appointment in the performance of VA-Approved Research utilizing VA resources at the VAMC or in VA-approved space.

5. I understand that the VA Office of General Counsel (OGC) will review the invention disclosure and will decide whether VA can and will assert an ownership interest. Every effort will be made to issue a decision within 40 days of receipt of a complete file. OGC will base its decision on whether VA has made a significant contribution to the invention, to include my use of VA facilities, VA equipment, VA materials, VA supplies, and VA personnel, as well as assessment of the potential of the invention.

6. If VA asserts an ownership interest based on my inventive contribution, then, subject to Paragraph 7 below, I agree to assign certain ownership rights I may have in such invention to the VA. I agree to cooperate with VA, when requested, in drafting the patent applications(s) for such invention and will thereafter sign any documents, recognizing VA's ownership, as required by the U.S. Patent and Trademark Office at the time the patent application is filed.

7. VA recognizes that I am employed or appointed at the entity named in paragraph 4 and have obligations to disclose and assign certain Invention rights to It. If that entity asserts an ownership interest. VA will cooperate with it to manage the development of the invention as appropriate.

8. If a Cooperative Technology Administration Agreement (CTAA) exists between the VA and the mentioned entity in paragraph 4, this Agreement will be implemented in accordance with the provisions of that CTAA.

Mahdi A. Shkoukani 12/3/01

Signature Date

Richard E Miller

Richard E. Miller, M.D. Date
ACOS/R&D

VA-WOC APPOINTEE INTELLECTUAL PROPERTY AGREEMENT

This agreement is made between Khaled Mansour and the Department of Veterans Affairs (VA) in consideration of my without compensation (WOC) appointment by the VA Medical Center, Detroit, Michigan (VAMC) and performing VA-Approved Research (as defined below) utilizing VA resources. This agreement is not intended to be executed by WOC appointees exclusively performing clinical services, attending services, or educational activities at the VAMC.

1. I hold a WOC appointment at the VAMC for the purpose of performing research projects, evaluated and approved by the VA Research and Development Committee (VA-Approved Research), at that VAMC.

2. By signing this agreement, I understand that, except as provided herein, I am adding no employment obligations to the VA beyond those created when I executed the WOC appointment.

3. I have read and understand the VHA Intellectual Property Handbook 1200.18 (attached) which provides guidance and instruction regarding Invention disclosures, patenting and the transfer of new scientific discoveries.

4. Notwithstanding that I am an employee or appointee at Wayne State University, I will disclose to VA any invention that I make while acting within my VA-WOC appointment in the performance of VA-Approved Research utilizing VA resources at the VAMC or in VA-approved space.

5. I understand that the VA Office of General Counsel (OGC) will review the invention disclosure and will decide whether VA can and will assert an ownership interest. Every effort will be made to issue a decision within 40 days of receipt of a complete file. OGC will base its decision on whether VA has made a significant contribution to the invention, to include my use of VA facilities, VA equipment, VA materials, VA supplies, and VA personnel, as well as assessment of the potential of the invention.

6. If VA asserts an ownership interest based on my inventive contribution, then, subject to Paragraph 7 below, I agree to assign certain ownership rights I may have in such invention to the VA. I agree to cooperate with VA, when requested, in drafting the patent applications(s) for such invention and will thereafter sign any documents, recognizing VA's ownership, as required by the U.S. Patent and Trademark Office at the time the patent application is filed.

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8. If a Cooperative Technology Administration Agreement (CTAA) exists between the VA and the mentioned entity in paragraph 4, this Agreement will be implemented in accordance with the provisions of that CTAA.

Signature Date

Richard E. Miller, M.D. Date
ACOS/R&D

60400038 .080203

CERTIFICATION

For Reporting of Inventions

I, M. SAFWAN BADR, hereby certify that the invention entitled Method to determine flow limitation and upper airway resistance patent application no.______________, was made by me on 1/1/02, while at the VA Medical Center John D. Dingell, while employed as (title of position) Staff physician

At the time of the invention (I did)(I did not) have a responsibility to perform research for VA, whether by VA research funding, VA employment or otherwise. (IMPORTANT: Explain further in paragraph 3 of the Report of Invention.) Other inventor(s) were ____________________

The invention was made:

1. During my official VA working hours	YES ✓	NO____
2. With a contribution by the VA of:		
(a) Facilities	YES ✓	NO____
(b) Equipment	YES ✓	NO____
(c) Materials	YES ✓	NO____
(d) Funds	YES ✓	NO____
(e) Information	YES ✓	NO____
(f) Time or services of other VA employees on official duty	YES____	NO ✓
3. The invention:		
(a) bears a direct relation to my VA research duties	YES ✓	NO____
(b) was made in consequence of my VA research duties	YES ✓	NO____
4. I am attaching remarks relating to the above	YES____	NO ✓

I attest that the responses above are accurate and correct

Signature: M. S. Badr (Inventor) — Date: 1/2/02

I attest that the responses above are accurate and correct

Signature: [signature] (Immediate Supervisor) — Date: 7/8/02

I attest that the responses above are accurate and correct

Signature: Richard E. Miller (ACOS R&D Office) — Date: 7/8/2002

G04B0038 . 080P02

CERTIFICATION
For Reporting of Inventions

I, KHALED . FALAH . MANSOUR, hereby certify that the invention entitled Method to determine flow limitation and Upper Airway resistance. patent application no.__________, was made by me on 1/1/02, while at the VA Medical Center John D. Dingell while employed as (title of position) Research Post Doc

At the time of the invention (I did)(I did not) have a responsibility to perform research for VA, whether by VA research funding, VA employment or otherwise. (IMPORTANT: Explain further in paragraph 3 of the Report of Invention.) Other inventor(s) were ____________________

The invention was made:

1. During my official VA working hours	YES ✓	NO____
2. With a contribution by the VA of:		
(a) Facilities	YES ✓	NO____
(b) Equipment	YES ✓	NO____
(c) Materials	YES ✓	NO____
(d) Funds	YES ✓	NO____
(e) Information	YES ✓	NO____
(f) Time or services of other VA employees on official duty	YES ✓	NO____
3. The invention:		
(a) bears a direct relation to my VA research duties	YES ✓	NO____
(b) was made in consequence of my VA research duties	YES ✓	NO____
4. I am attaching remarks relating to the above	YES____	NO ✓

I attest that the responses above are accurate and correct

Signature: Khaled Mansour — 7-5-02
(Inventor) — Date

I attest that the responses above are accurate and correct

Signature: [signature] — 7/8/02
(Immediate Supervisor) — Date

I attest that the responses above are accurate and correct

Signature: [signature] — 7/8/02
(ACOS R&D Office) — Date

CERTIFICATION
For Reporting of Inventions

I, James A. Rowley, MD, hereby certify that the invention entitled Method to determine flow limitation & upper airway resistance patent application no ________, was made by me on 1/1/02, while at the VA Medical Center John D. Dingell, while employed as (title of position) Consultant.

At the time of the invention (I did)(I did not) have a responsibility to perform research for VA, whether by VA research funding, VA employment or otherwise (IMPORTANT· Explain further in paragraph 3 of the Report of Invention.) Other inventor(s) were ________

The invention was made:

	YES	NO
1. During my official VA working hours	✓	
2. With a contribution by the VA of:		
(a) Facilities	✓	
(b) Equipment	✓	
(c) Materials	✓	
(d) Funds	✓	
(e) Information	✓	
(f) Time or services of other VA employees on official duty	✓	
3. The invention:		
(a) bears a direct relation to my VA research duties	✓	
(b) was made in consequence of my VA research duties	✓	
4. I am attaching remarks relating to the above		✓

I attest that the responses above are accurate and correct

Signature: [signature] (Inventor) — Date 7/8/02

I attest that the responses above are accurate and correct

Signature: [signature] (Immediate Supervisor) — Date 7/8/02

I attest that the responses above are accurate and correct

Signature: Richard E. McClean (ACOS R&D Office) — Date 7/8/02

60400038 .080202

CERTIFICATION
For Reporting of Inventions

I, MAHDI A. SHKOUKANI, hereby certify that the invention entitled Method to determine flow limitation and upper airway resistance patent application no.__________, was made by me on 1/1/02, while at the VA Medical Center John D. Dingell, while employed as (title of position) Research Assistant.

At the time of the invention (I did)(I did not) have a responsibility to perform research for VA, whether by VA research funding, VA employment or otherwise. (IMPORTANT: Explain further in paragraph 3 of the Report of Invention.) Other inventor(s) were __________

The invention was made:

	YES	NO
1. During my official VA working hours	✓	
2. With a contribution by the VA of:		
(a) Facilities	✓	
(b) Equipment	✓	
(c) Materials	✓	
(d) Funds	✓	
(e) Information	✓	
(f) Time or services of other VA employees on official duty		✓
3. The invention:		
(a) bears a direct relation to my VA research duties	✓	
(b) was made in consequence of my VA research duties	✓	
4. I am attaching remarks relating to the above		✓

I attest that the responses above are accurate and correct

Signature: Mahdi A. Shkoukani (Inventor) — Date: 7/5/02

I attest that the responses above are accurate and correct

Signature: [signature] MD (Immediate Supervisor) — Date: 7/8/02

I attest that the responses above are accurate and correct

Signature: Gerhard E. McClov (ACOS R&D Office) — Date: 7/8/2002

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SLEEP RESEARCH LABORATORY

WAYNE STATE UNIVERSITY
DEPARTMENT OF INTERNAL MEDICINE

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NOTES/COMMENTS:

A Mathematical Model to Detect Inspiratory Flow Limitation During Sleep

Final Accepted Version

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Abstract

The physiologic significance of inspiratory flow limitation (IFL) has recently been recognized but methods of detecting IFL can be subjective. We sought to develop a mathematical model of the upper airway pressure-flow relationship that would objectively detect flow-limitation. We present a theoretical discussion that predicts that a polynomial function, $F(P) = AP^3 + BP^2 + CP + D$, where $F(P)$ is flow and P is supraglottic pressure, best characterizes the pressure-flow relationship and allows for the objective detection of IFL. In Protocol #1, Step #1, we performed curve-fitting of the pressure-flow relationship of 20 breaths to 5 mathematical functions and found that highest correlation coefficients (R^2) for quadratic (0.88±0.10) and polynomial (0.91±0.05, $p<0.05$ for both compared to the other functions) functions. In Step #2, we performed error-fit calculations on 50 breaths comparing the quadratic and polynomial functions and found that the error fit was lowest for the polynomial function (3.3±0.06% v. 21.1±19.0%, $p<0.001$). In Protocol #2, we performed sensitivity/specificity analysis on 2 sets of breaths (50 and 544 breaths) comparing the mathematical determination of IFL to manual determination. Mathematical determination of IFL had high sensitivity, specificity and positive predictive value (>99% for each). We conclude that a polynomial function can be used to predict the relationship between pressure and flow in the upper airway and objectively determine the presence of IFL.

Key Words: upper airway, polynomial equation, pressure-flow relationship

Introduction

Sleep-disordered breathing can manifest as a spectrum from inspiratory flow-limitation (IFL) to hypopneas and apneas. While clinicians and investigators have long recognized the clinical importance of apneas and hypopneas, the importance of IFL in the spectrum of SDB has only recently been recognized with the recognition of the upper airway resistance syndrome (UARS) (5). UARS is characterized by repetitive episodes of IFL and decreases in esophageal pressure leading to recurrent arousals (8). The repetitive flow limitation events have been associated with excessive daytime sleepiness (5) and changes in blood pressure (6), clinical and physiological responses that have also been noted with apneas and hypopneas. In addition, our research laboratory has shown that the presence of IFL in otherwise apparently normal subjects can predict different responses to mechanical and chemical interventions during sleep (2;4).

The increasing clinical and physiologic significance to the presence of IFL necessitates that there be an objective and reproducible method to detect IFL. Investigators have shown that flow-limitation events can be detected without esophageal manometry (1;7) but the detection of flow-limitation in these studies is based upon visual inspection of the flow contour only, increasing the potential for a subjective interpretation of the data. In studies from our laboratory, we have determined if a breath demonstrates IFL by either visual analysis (2) or manual analysis of the pressure-flow loop (Figure 1; see Methods below for definitions) (4;17). Manual analysis of the pressure-flow loop is a time-consuming task and despite a clear definition of IFL we have found there to be frequent interscorer differences in determining if a breath demonstrates IFL and that some breaths are not easily characterized as either IFL or non-inspiratory flow limited (NIFL). We hypothesized that a mathematical model may provide a method for the objective detection of IFL. Previous investigators have shown that the pressure-

flow relationship of the upper airway can be modeled mathematically (9;16;20) but these investigators did not specifically develop a model to detect flow-limitation. Therefore, the objective of the work presented in this paper was to develop a mathematical model of the pressure-flow relationship in the upper airway that would detect flow-limitation with precision, objectiveness and reproducibility.

Theory and Hypothetical Considerations

We consider a steady homogenous flow in a circular cylinder (the upper airway), with the assumption that the flow of air in the upper airway will expand without the loss or gain of heat. Consider a streamline of air which connects two points M_1, the upstream pressure, which is atmospheric pressure in our model, and M_2, the downstream pressure, which is equivalent to supraglottic pressure in our model. For each point, there is a density (ρ), pressure (P), area (A), velocity (V) and flow (F) that characterizes that point. In the modeling that follows, it should be noted that the goal is determination of the flow of the upper airway at the downstream pressure point, M_2. Flow, which is constant throughout the upper airway, is given by:

$$F = \rho_1 A_1 V_1 = \rho_2 A_2 V_2 \quad (1)$$

Solving for V_1:

$$V_1 = \frac{\rho_2 A_2}{\rho_1 A_1} V_2 = \Omega V_2 \quad (2)$$

where

$$\Omega = \frac{\rho_2 A_2}{\rho_1 A_1} = \frac{A_2}{A_1}$$

The Bernoulli or energy equation for homogenous fluid such as air, on one streamline, through M_1, M_2 and neglecting the effect of gravity is:

$$\frac{P_1}{\rho_1} + \frac{1}{2} V_1^2 = \frac{P_2}{\rho_2} - \frac{1}{2} V_2^2 \quad (3)$$

Because air is a compressible, we need to consider the heat kinematic ratio $\frac{\gamma}{\gamma-1}$. If we set the kinematic heat ratio as: $K=\frac{\gamma}{\gamma-1}$, then we can rewrite equation (3) as:

$$K\frac{P_1}{\rho_1}+\frac{1}{2}V_1^2=K\frac{P_2}{\rho_2}+\frac{1}{2}V_2^2 \quad (4)$$

Because the path of the upper airway is short then we may assume $\rho_1 \cong \rho_2 = \rho$. We can then rearrange equation 4 as:

$$P_1-P_2=\frac{\rho}{2K}\left(V_2^2-V_1^2\right) \quad (5)$$

Substituting V_1^2 from equation 2:

$$P_1-P_2=\frac{\rho}{2K}\left(V_2^2-\Omega^2V_2^2\right) \quad (6)$$

Solving for V_2^2:

$$V_2^2=2K\frac{\left(P_1-P_2\right)}{\rho\left(1-\Omega^2\right)} \quad (7)$$

Squaring both sides of equation 1, we can obtain the flow squared at point M_2:

$$F^2=\rho^2A_2^2V_2^2 \quad (8)$$

Substituting for V_2^2 from equation 7:

$$F^2=\frac{2\rho A_2^2K}{\left(1-\Omega^2\right)}\left(P_1-P_2\right) \quad (9)$$

Rearranging:

$$F^2=\frac{2\rho A_2^2K}{\left(1-\Omega^2\right)}P_1\left(1-\frac{P_2}{P_1}\right) \quad (10)$$

Taking the square root of both sides of equation 10, we obtain:

$$F=\left(\frac{2\rho A_2^2KP_1}{(1-\Omega^2)}\right)^{\frac{1}{2}}\left(1-\frac{P_2}{P_1}\right)^{\frac{1}{2}} \quad (11)$$

Let

$$G=\left(\frac{2\rho A_2^2KP_1}{(1-\Omega^2)}\right)^{\frac{1}{2}}$$

Therefore, flow through a streamline between two points, M_1 and M_2, is given by:

$$F=G\left(1-\frac{P_2}{P_1}\right)^{\frac{1}{2}} \quad (12)$$

Using Newton's expansion law:

$$(1+X)^N=1+NX+\frac{N(N-1)}{2!}X^2+\frac{N(N-1)(N-2)}{3!}X^3+\ldots$$

We obtain:

$$F=G+\frac{G}{2P_1}P_1+\frac{G}{8P_1^2}P_2^2-\frac{3G}{48P_1^3}P_2^3+\ldots \quad (13)$$

If we let, $A=\frac{3G}{48P_1^3}, B=\frac{G}{8P_1^2}, C=\frac{G}{2P_1}, D=G$

we can then substitute these coefficients into equation 13 to get a polynomial function that approximates flow [$F(P)$] in terms of the supraglottic pressure. For this function, we assume that P_1 is atmospheric pressure, which is a constant, and P_2 = P, which we now define as the supraglottic pressure:

$$F(P)=AP^3+BP^2+CP+D \quad (14)$$

Per Newton's expansion law, the relationship between pressure and flow could also be predicted by a quadratic equation:

$$F(P)=AP^3+BP+C \quad (15).$$

However, the nature of a polynomial function predicts that a polynomial function would be expected to better estimate the pressure-flow relationship than the quadratic function for flow-limited breaths. This is because for IFL breaths, the polynomial function is characterized by two deflections, as illustrated in Figure 2. A two deflection relationship will better approximate the measured pressure-flow relationship of IFL breaths, which are characterized by a point of maximum flow, followed by a decrease and plateau in flow (Figure 1). The quadratic function, however, is characterized by only one deflection (see Figure 2), and therefore, does not as closely approximate the measured pressure-flow relationship of IFL breaths.

While performing the initial curve-fitting analysis (see Methods below), we noted that the nature of the polynomial function, in contrast to the quadratic function, would allow for the objective differentiation of IFL and NIFL breaths. In particular, we noted that for the polynomial function, the maximal flow of the predicted relationship usually was at same pressure as the measured maximal flow. In contrast, the predicted maximal flow for the quadratic function would be at a more negative pressure. To objectify these observations, we hypothesized that we could determine the presence of flow-limitation by examining derivative of the polynomial function, which is represented by the slope of the pressure-flow relationship. The derivative of the polynomial function is:

$$\frac{dF}{dP}=3AP^2+2BP+C \quad (15)$$

Theoretically, for non-flow limited breaths, flow would continue to increase beyond the point of maximal flow if there were further decreases in supraglottic pressure. Therefore, the derivative of the polynomial function (or the slope of the pressure-flow curve) at the actual maximal flow is negative. This is illustrated in Figure 3 (panel A) which shows a NIFL breath (grey solid line)

and the theoretic relationship using the polynomial function (black dashed line). At the measured maximal flow, the slope of the theoretic pressure-flow relationship is negative, as illustrated in Panel B However, for breaths that demonstrate inspiratory flow limitation, there are no further increases in flow despite decreasing supraglottic pressure (Figure 3, Panel C). Therefore, the slope or derivative of the polynomial function at the measured maximal flow is either zero or positive for flow-limited breaths (Figure 3, panel D). Therefore, at maximal flow, two cases can be determined from equation 15 If 1) $\frac{dF}{dP} < 0$, the breath is nonflow-limited; and 2) $\frac{dF}{dP} > 0$ or $\frac{dF}{dP} = 0$, the breath is flow-limited.

By a similar analysis we hypothesized that the derivative of the quadratic function cannot be used to determine if the pressure-flow relationship demonstrates flow limitation. The derivative of the quadratic function is given as:

$$\frac{dF}{dP} = 2AP + B \quad (17)$$

However, if the quadratic function is used to characterize the pressure-flow relationship (black dash-dot lines in Figure 3, Panels A and C), the derivative of the quadratic function cannot be used to distinguish between non-flow limited and flow-limited breaths. This is illustrated in Figure 3 (panels B and D) which shows that the derivative of the quadratic equation will be negative for both types of breaths. In other words, $\frac{dF}{dP} < 0$ for all breaths.

In summary, theoretical considerations indicate that the relationship between flow and supraglottic pressure in the upper airway can be characterized by either a quadratic or polynomial function However, based upon the theoretical considerations, we hypothesized that the polynomial function was the better of the two functions to mathematically model the upper

airway because it would provide the best fit compared to the actual pressure-flow relationship and use of its derivative would provide an objective and accurate method for the detection of inspiratory flow limitation.

Methods

Measurements and manual determination of flow limitation

For each breath, airflow (V) was measured by a pneumotachometer (Model 3700A, Hans Rudolph Inc.) attached to a nasal mask. Supraglottic airway pressures were measured using a pressure-tipped catheter (Model TC-500XG, Millar Co.) threaded though the mask and positioned in the oropharynx just below the base of the tongue. Correct placement in the hypopharynx was confirmed by advancing the catheter tip for 2 cm after it disappeared behind the tongue.

The sequence of analysis is illustrated in Figure 4. During the studies, airflow and supraglottic pressure were recorded simultaneously with Biobench data acquisition software (National Instruments, Austin, TX) on a separate computer (Figure 4, Panel A). For each breath, the onset of inspiration was defined as the sampling point at which $V_I = 0$. On the rare occurrence in which there was a shift in baseline, the nadir flow was determined and the flow values shifted appropriately. Because the Millar catheter provides relative pressures, P_{SG} was set to zero for the inspiration onset sampling point and the remaining values for the breath were calculated. A pressure flow loop was generated (Figure 4, Panel B) and the loop was analyzed for the presence of inspiratory flow limitation (IFL) (Figure 1). A breath was labeled IFL if there was a 1 cmH_2O or greater decrease in supraglottic pressure without any corresponding increase

in flow during inspiration. If the flow-pressure relationship did not meet this criterion, the breath was labeled as non-flow limited (NIFL).

All analyzed breaths in the following protocols were obtained during Stage 2 NREM sleep. Breaths from wakefulness were not analyzed as IFL is not observed during wakefulness. As slow wave and REM sleep are uncommonly observed in the heavily instrumented subjects, breaths from these stages could not be analyzed. In addition, only breaths free from artifact were included in the analysis. All breaths were obtained from healthy, adults with no sleep-related complaints who had volunteered for research studies in the laboratory. All subjects were free of sleep-disordered breathing, as measured by apneas and hypopneas, on baseline polysomnography. Demographics of the subjects are presented within each protocol.

Protocol #1: Does the polynomial function best predict the relationship between pressure and flow in the upper airway?

Step 1: Curve Fitting: To model the upper airway mathematically, we performed a curve fitting analysis using Sigma Stat 2.0 software (Figure 4, Panel C and Figure 5, Panel A). The purpose of this analysis was to determine which of five regression equations (Table 1) best estimated inspiratory flow (the dependent variable) as a function of supraglottic pressure (the independent variable). This process is similar to performing a linear regression, in which the predicted relationship can be given by the equation: $F(P) = AP + B$. However, since the pressure-flow relationship is not linear, we used 5 non-linear regression functions. The first two are derived from the theoretical considerations above: quadratic and polynomial. The third, a single-term hyperbolic, has previously been proposed as an accurate predictor of the pressure-flow relationship (9). In addition, we analyzed 2 additional functions double-term hyperbolic and

exponential (13). Neither the pressure or flow values were transformed prior to the curve fitting (14). This analysis was performed on 20 breaths, 10 NIFL, 10 IFL derived from 4 subjects (1 male, 3 females, mean age 22 ± 3 yrs, mean BMI 23.0 ± 3.0 kg/m^2). For each calculated function, we determined the coefficient of determination (R^2), which indicates how much of the variability in one variable (flow) is explained by knowing the value of the other (supraglottic pressure) (12). The R^2 for IFL and NIFL breaths were compared between the five functions using one-way repeated measures analysis of variance (ANOVA), with breath number as the repeated measure and the function as the factor for comparison. If there was a significant difference between the groups, a Student-Newman-Keuls test was performed to detect between group differences with $p<0.05$ set as the level for a significant test. The same test was performed on the combined groups of breaths.

<u>Step 2: Error Fit:</u> To determine the degree of approximation between the pressure-flow relationship derived from either the quadratic or polynomial function to the actual pressure-flow relationship, we determined the error-fit for 50 breaths, 25 each NIFL and IFL derived from 8 subjects (5 males, 3 females, mean age 25 ± 4 yrs, mean BMI 26.2 ± 4.8 kg/m^2). Only the quadratic and polynomial functions were studied based upon the results of the curve fitting analysis (see Results). An illustration of the concept of error-fit is given in Figure 5. The right panel shows the actual pressure-flow relationship for an IFL breath (solid line) and the predicted pressure-flow relationship using either the quadratic function (dashed line). The gray-shaded areas show the difference between the two relationships The smaller the gray-shaded area, the smaller the error-fit and the more closely the predicted relationship approximates the actual

pressure-flow relationship. The error-fit is a mathematical representation of this gray-shaded area. Mathematically, error fit is defined as:

$$100(\sum_{i}^{k} 1-(y_k - y_i)\quad(18)$$

where $\sum_{i}^{k}$ is the summation of a series of points, y_k represents the points in the original function and y_i represents the points in the fitted function (14). Using this formula, as the predicted pressure-flow relationship more closely approximates the actual relationship, the error-fit or difference between the two relationships decreases. The error-fit for IFL and NIFL breaths were compared between the five functions using one-way repeated measures analysis of variance (ANOVA), with breath number as the repeated measure and the function as the factor for comparison. If there was a significant difference between the groups, a Student-Newman-Keuls test was performed to detect between group differences with $p<0.05$ set as the level for a significant test. The same test was performed on the combined groups of breaths.

Protocol #2: Does the polynomial function objectively detect flow limitation?

Step 1: Using the same 50 breaths on which we determined the error-fit, we determined the slope of the polynomial function at the measured maximal flow for the polynomial equation (Figure 4, Panel D). Per the hypothesis, if the slope at the measured maximal flow was <0, we labeled the breath NIFL; if the slope at the measured maximal flow was ≥0, we labeled the breath IFL. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of IFL breaths by the polynomial model compared to the standard method (described at the beginning of the Methods section) using standard formulas (18).

To confirm the hypothesis that the slope at the measured maximal flow for the quadratic equation would be negative for both IFL and NIFL breaths, we determined the slope at the measured maximal flow for the same 50 breaths. We report the proportion of NIFL and IFL breaths with a negative slope.

Step 2 To validate the results, we then determined the slope of the polynomial function at the measured maximal flow using the polynomial equation for 544 randomly selected breaths from 20 subjects without sleep-disordered breathing as measured by apneas and hypopneas (10 males, 10 females, mean age 30 ± 8 yrs, mean BMI 25.2 ± 4.3 kg/m²). Applying the hypothesis, we labeled each breath as NIFL or IFL. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value for the detection of IFL breaths by the polynomial model compared to the standard method using standard formulas (18).

Results

Protocol #1

Step 1: Curve Fitting: The results of the curve fitting are presented in Table 2. There was a significant difference between the R^2 values when all the breaths are combined and for the NIFL and IFL breaths when analyzed separately ($p<0.001$ for all three comparisons). For NIFL breaths, post-hoc testing showed that R^2 was significantly larger for the polynomial function compared to all other functions and that the quadratic function had a larger mean R^2 compared to other three functions. For IFL breaths, there was no difference in the mean R^2 values between the quadratic, polynomial and double hyperbolic functions. All three functions had larger mean R^2 values compared to the single-hyperbolic and exponential functions. For all the breaths

combined, the mean R^2 was highest for the polynomial function; in addition, the R^2 values were higher for the quadratic equation compared to the other three functions. In summary, the polynomial and quadratic functions had better fits to the data than the single- and double-term hyperbolic and exponential functions. Therefore, further analysis was performed only on the quadratic and polynomial functions.

Step 2: Error-Fit: Representative graphs depicting the relationship between the actual pressure-flow curve and the curve as predicted by either the quadratic or polynomial equations for one IFL and one NIFL breath are illustrated in Figure 3. As can be seen, there is more overlap (less error) between the actual and predicted curves for the polynomial function than for the quadratic function. For the total group of 50 breaths, the error fits for the polynomial function were smaller on average than the quadratic function for the IFL breaths (2.0±2.7% v. 25.0±22.2%, $p<0.001$), NIFL breaths (4.0±7.7% v 16.0±14.0%, $p=0.003$) and for all breaths combined (3.3±0.05% v. 21.1±19.0%, $p<0.001$).

In summary, in Protocol #1, we showed that curve-fitting the pressure-flow relationship in the upper airway will result in a tight fit (high R^2) of the data only for the quadratic and polynomial functions. However, when using a test that determines the degree of correlation between the actual and experimental relationships (error-fit), only the polynomial function accurately predicts the pressure-flow relationship.

Protocol #2

Step 1: The sensitivity, specificity, PPV and NPV for the detection of flow limitation in the initial 50 breaths using the polynomial function is summarized in Table 3. As the table

illustrates, using the slope at maximal flow of the polynomial equation results in both high sensitivity and specificity for the determination of IFL breaths. PPV and NPV were also high. For the quadratic function, we confirmed that the majority of breaths of both NIFL (24 of 25, 96%) and IFL (22 of 25, 88%) IFL breaths had a negative slope, indicating that the quadratic function would be unhelpful in detecting IFL breaths

Step 2. In the larger group of breaths, sensitivity and specificity remained high (Table 3, right column), as did the PPV and NPV.

In summary, in Protocol #2, we performed a sensitivity/specificity analysis of the use of polynomial function to detect IFL breaths compared to the standard method using a pressure-flow loop. This analysis indicates that the polynomial function has an excellent ability to predict the presence of flow-limitation in the pressure-flow relationship. In contrast, the quadratic function cannot be used to distinguish between IFL and NIFL breaths.

Discussion

There are two major findings of this study. First, a polynomial equation, $F(P) = AP^3 + BP^2 + CP + D$, provides an estimation of the upper airway pressure-flow relationship with relative precision compared to other mathematical equations. Second, the derivative of this equation can be used to objectively and precisely determine the presence of inspiratory flow limitation. The main requirement for the accurate determination of IFL using the polynomial function is a continuous and simultaneous measurement of flow and supraglottic pressure.

The relationship between flow and pressure in the upper airway during wakefulness was first described by Rohrer using the equation: $P = K_1{*}V + K_2{*}V^2$, where V is flow and K_1 and K_2

are constants (16). Hudgel and colleagues noted that the pressure-flow relationship during sleep was curvilinear and therefore less likely to be adequately described by the Rohrer equation. Instead, this group determined that a hyperbolic function (see Table 1) better characterized the upper airway pressure-flow relationship during sleep, as indicated by a correlation coefficient of 0.89 compared to 0.55 for the Rohrer equation (9). They hypothesized that the characterization was better because the hyperbolic equation approximated the pressure-flow relationship for both NIFL and IFL breaths. Similarly, Tamisier and colleagues recently found that the hyperbolic equation better characterized by the pressure-flow relationship, as evidenced by larger Pearson's square correlations for all breaths analyzed as well as for the subset of IFL breaths(20). In contrast, we found that a 3-term polynomial function best characterized the pressure-flow relationship during sleep. In addition, we found that a hyperbolic function provided a poor characterization of the pressure-flow relationship.

There are possible explanations for the different findings. First, while the Rohrer equation is a polynomial function, it is only a 2-term quadratic function. Our data indicate that a 3-term function provides a better fit of the pressure-flow relationship than a 2-term function. Neither of the previous groups tested a 3-term polynomial function. Second, it should be noted that we performed our curve fitting on the raw pressure-flow data. Therefore, our pressure points were negative in value at the time of the curve fitting. The other groups used pressure values that had been transformed to positive pressures prior to curve fitting. The importance of this difference is illustrated in Figure 6. As can be seen, if positive values are used for pressure values, a hyperbolic curve does closely approximate the actual pressure-flow relationship (Panel B). However, if negative values are used, a hyperbolic curve does not approximate the relationship (Panel A). We believe that our use of the negative values for pressure is proper because the

mathematical equations for curve fitting were derived to determine the relationship between predicted and observed (or actual), not transformed, variables (14).

Limitation of Methods

The theoretical approach presented at the beginning of the paper has one major potential limitation. In particular, to apply Newton's expansion law, we had to create a constant, *G*, that contains multiple parameters including density, area, atmospheric pressure and the kinematic heat ratio. Therefore, for *G* to be a constant, these parameters must be assumed to be constant during flow between points M_1 and M_2. The assumption that density and the kinematic heat ratio are constants has been made by others (11) and is based upon thermodynamic principles (19). Area was also been assumed to be a constant by Rohrer (16). However, it has been shown that nasopharyngeal area will change during a flow-limited breath (10). In our model, the downstream area (A_2) is the area at the level of the supraglottic pressure catheter and we do not know of a study that shows that area of the supraglottic space changes during inspiration in normal subjects. In contrast, oropharyngeal and hypopharyngeal area have been shown to change in patients with sleep apnea (15). Therefore, we we cannot be certain that *G* is a constant during any given breath. Nevertheless, the excellent agreement between the measured data and polynomial function data supports the validity of the assumptions, including that area is a constant, that were made while developing the theoretical background.

To ascertain the accuracy of mathematical detection of IFL, we had to use a "benchmark" for detection of flow limitation. We chose an arbitrary degree of dissociation between pressure and flow for 1cm decrement in supraglottic pressure, based mainly on our ability to identify such decrement in pressure. However, the physiologic consequences of such mild degree of

inspiratory flow limitation are not known. Conversely, mathematical methods and visual methods were remarkably reproducible indicating that our choice of parameter was valid for the recognition of the phenomenon. Our study provides an objective operational definition, which can be used in future studies to ascertain physiologic relevance.

Inspiratory flow limitation in our study was evaluated as a dichotomous variable. However, deviation from linearity between flow and pressure is a continuous variable. Our method detects flow limitation as defined by a plateau in flow only; any other alinear flow profile is classified as non-flow limitation. One could argue that changes in the slope of the pressure-flow relationship indicate pharyngeal narrowing and turbulent flow. In fact, these were the breaths missed by the mathematical equation. However, we doubt the physiologic significance of deviation from linearity without true flow limitation.

Finally, detection of inspiratory flow limitation in our study required the use of supraglottic pressure measurement via a pharyngeal catheter and quantitative flow measurement using a sealed mask and a pneumotachometer. This combination is rather intrusive and may not be feasible for routine clinical use. Whether IFL can be detected from the flow versus time profile is yet to be determined.

Implications

The ability to detect inspiratory flow limitation objectively may have significant relevance to the diagnosis of sleep-disordered breathing (SDB). The description of UARS expanded the spectrum of SDB by including patients without episodes of apnea or identifiable hypopnea (5). The main features of UARS are the recurrent arousal due to repetitive episodes of IFL and decreases in esophageal pressure. Recent studies have shown a moderate correlation

between the number of respiratory events, including periods of IFL, and daytime sleepiness (7). Unfortunately, detection of inspiratory flow limitation was based on subjective visual detection of a square flow profile without pressure measurements. Conversely, manual analysis of the pressure-flow loop is laborious and fraught with subjective pitfalls. We have shown that the polynomial function is both highly sensitive and specific for the determination of the presence of flow-limitation. Thus, our method can be used on a large number of breaths in an automated fashion and may be useful in future studies that assess the relationship between SDB and other variables. For instance, we have recently shown that the percentage of breaths that are flow limited is related to BMI and upper airway resistance (17) and to the presence of long-term facilitation (3). Therefore, we hypothesize that a determination of the presence of flow-limitation may provide an alternative metric to assess the relationship between SDB and daytime consequences such as excessive daytime sleepiness and cardiovascular morbidity, particularly in non-apneic forms of the syndrome.

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Figure Legends

Figure 1: Pressure-flow loops illustrating a non-flow limited (NIFL) and a flow limited (IFL) breath. A breath was labeled IFL if there was a 1 cmH_2O or greater decrease in supraglottic pressure without any corresponding increase in flow during inspiration.

Figure 2: Graphical representation of the mathematical nature of polynomial (left panel) and quadratic (right panel) functions. The polynomial function is characterized by two deflections (labeled as 'Max' and 'Min') while the quadratic function is characterized by one deflection (labeled 'Max').

Figure 3 Graphical representation of the theoretic considerations regarding the ability of the polynomial and quadratic functions to distinguish between NIFL (Panels A, B) and IFL breaths (Panels C, D). Panels A and C illustrate the measured pressure-flow relationship (solid gray line) and the theoretic polynomial (black solid line) and quadratic (black dash-dot line) relationships. The vertical straight line in all panels is at the measured maximal flow. Panels B and D illustrate the slopes of the predicted functions at increasing P_{SG} values. The slope at the measured maximal flow for both the polynomial (circle) and quadratic functions (square) remains negative for NIFL breaths (Panel B). The slope of the polynomial function at measured maximal flow becomes positive for IFL breaths while the slope of the quadratic function remains negative (Panel D).

Figure 4: Sequence of data analysis. Panel A: example of three breaths from the raw tracing from a polygraph. The data analysis was performed on the middle (boxed) breath. Panel B:

Pressure-flow loop of the indicated breath. The selected breath demonstrates flow-limitation as there is no increase flow despite a >1 cmH_2O decrease in P_{SG}. Panel C: Curve-fitting analysis graph shows only the ascending limb of the inspiratory portion of the pressure-flow loop (solid line) and the fitted polynomial curve (dashed line) The equation for the fitted curve is $F(P) = -0.0005*P^3 - 0.0151*P^2 - 0.1137*P + 0.0338$. Panel D: Determination of flow-limitation: graph shows the plot of the slope of the polynomial function v. P_{SG}. For this breath, $Slope = -0.0015*P^2 - 0.0302*P - 0.1137$. Since the slope of the polynomial function is 0.001 (≥ 0) at measured maximal flow (vertical line), the breath is characterized as IFL by the model. Abbreviations: EEG: electroencephalogram; P_{SG}: supraglottic pressure.

Figure 5: Illustrations of the analyses done in Protocol #1. A. An example of curve fitting. The figure shows the (open circles) and the predicted pressure-flow relationships if the points are fitted to a quadratic function (solid line) or the two-term hyperbolic function (dashed line). B. An example of error-fit The figure shows the actual (solid line) and predicted (dashed line) pressure-flow relationships The predicted relationship uses the quadratic function. The shaded area is the graphical representation of the mathematical formula for error fit given in the text.

Figure 6: Panel A: Graphic representation of an IFL breath (solid line) and the fitted hyperbolic function (dashed line) when flow is fit to raw pressure data. Panel B: Graphic representation of the same IFL breath (solid line) and the fitted hyperbolic function (dashed line) when flow is fit to pressure data transformed to the absolute value. Note that in Panel A, a hyperbolic curve provides a poor representation for the actual pressure-flow relationship while in

Panel B, a hyperbolic curve provides a reasonable representation of the pressure-flow relationship

Table 1: Functions used for Curve Fitting

Function	Equation
One-term hyperbolic	$F(P)=\frac{AP}{B+P}$
Two-term hyperbolic	$F(P)=\frac{AP}{B+P}+\frac{CP}{D+P}+FP$
Exponential	$F(P)=Ae^{(-BP)}+Ce^{(-DP)}$
Quadratic	$F(P)=AP^2+BP+C$
Polynomial	$F(P)=AP^3+BP^2-CP+D$

For each function: F(P): flow as a function of pressure, A, B, C, D and F are coefficients; e is the exponential mathematical constant (~2.78).

Table 2: R^2-values for the Various Functions

	Quadratic	Polynomial	Single-hyperbolic	Double-hyperbolic	Exponential
IFL Breaths	0.85±0.10	0.90±0.06	0.61±0.14	0.79±0.13	0.55±0.32
NIFL Breaths	0.89±0.06	0.92±0.04	0.54±0.20	0.70±0.24	0.79±0.24
All Breaths	0.88±0.08	0.91±0.05	0.57±0.17	0.78±0.19	0.67±0.30

See text for statistical analysis

Table 3 Sensitivity/Specificity Analysis

	Development Breaths (n=50)	Validation Breaths (n=544)
Sensitivity	100	99
Specificity	100	99
PPV	100	97
NPV	100	99

PPV: positive predictive value; NPV: negative predictive value

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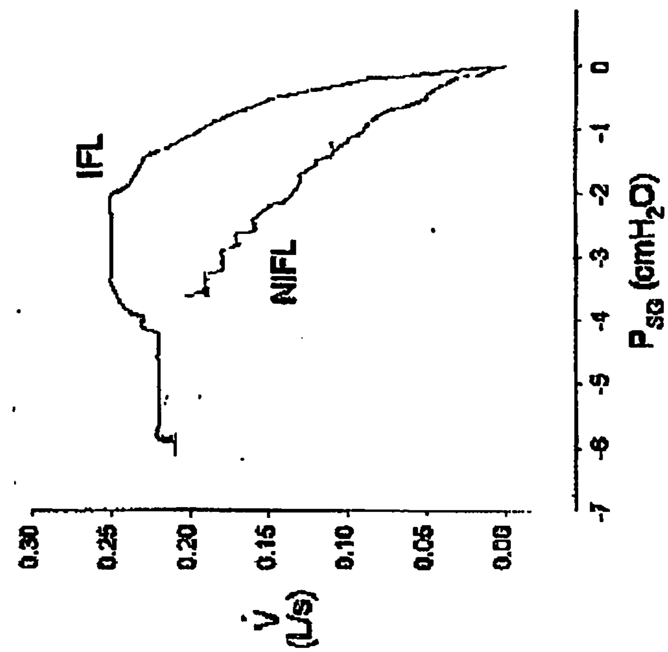


Figure 1

Figure 2

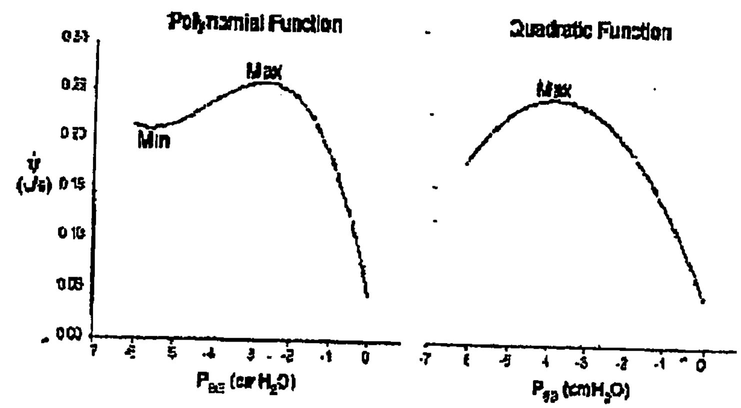

Polynomial Function
Max
Min
Quadratic Function
Max
0.00
0.05
0.10
0.15
0.20

Figure 3

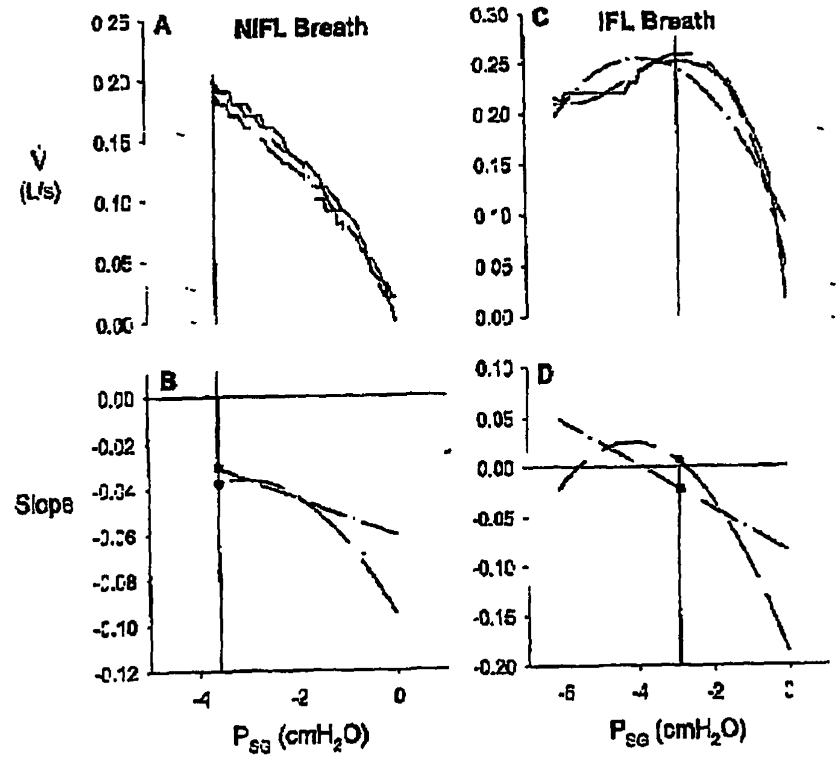
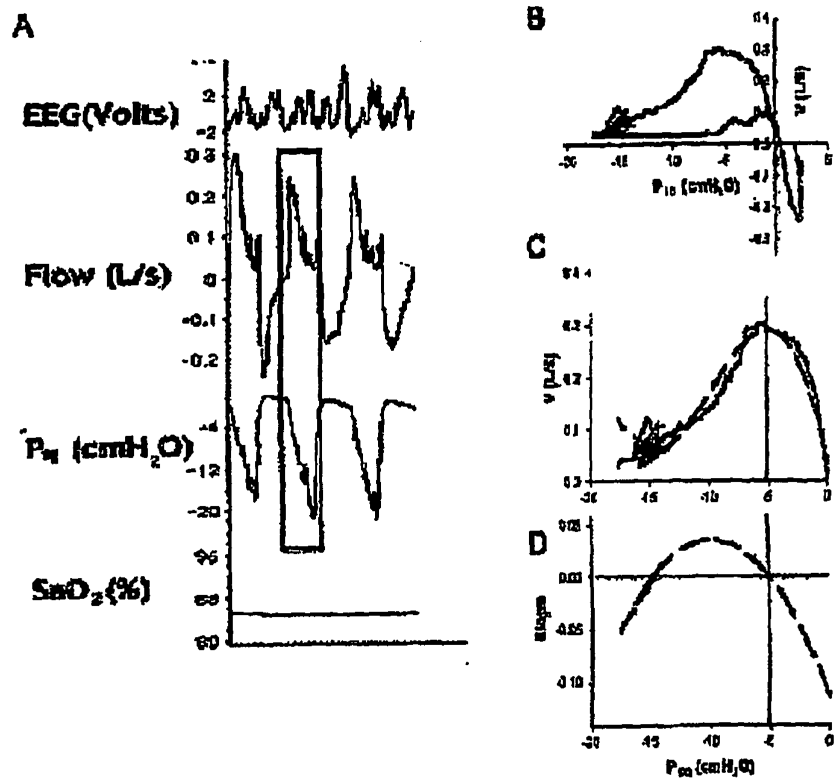

A
NIFL Breath
B
C
IFL Breath
D
V̇
(L/s)
Slope
PSG (cmH2O)
PSG (cmH2O)
0.25
0.20
0.15
0.10
0.05
0.00
-0.02
-0.04
-0.06
-0.08
-0.10
-0.12
-4
-2
0
0.30
0.25
0.20
0.15
0.10
0.05
0.00
0.10
0.05
0.00
-0.05
-0.10
-0.15
-0.20
-6
-4
-2
0

Figure 4



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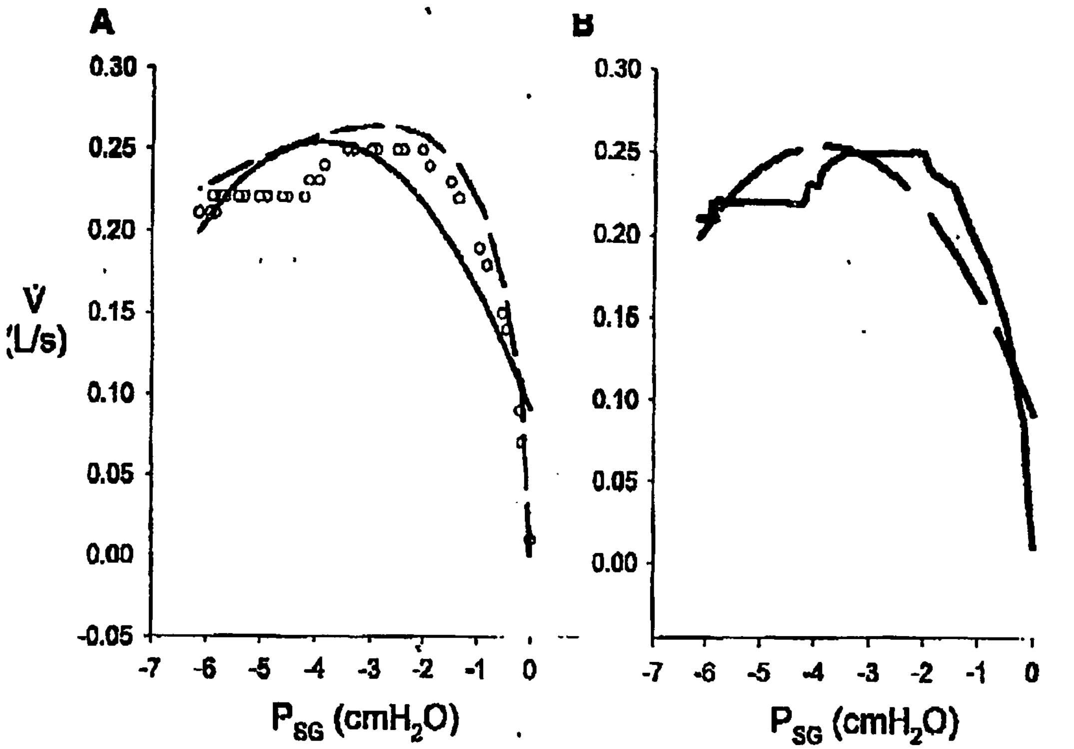
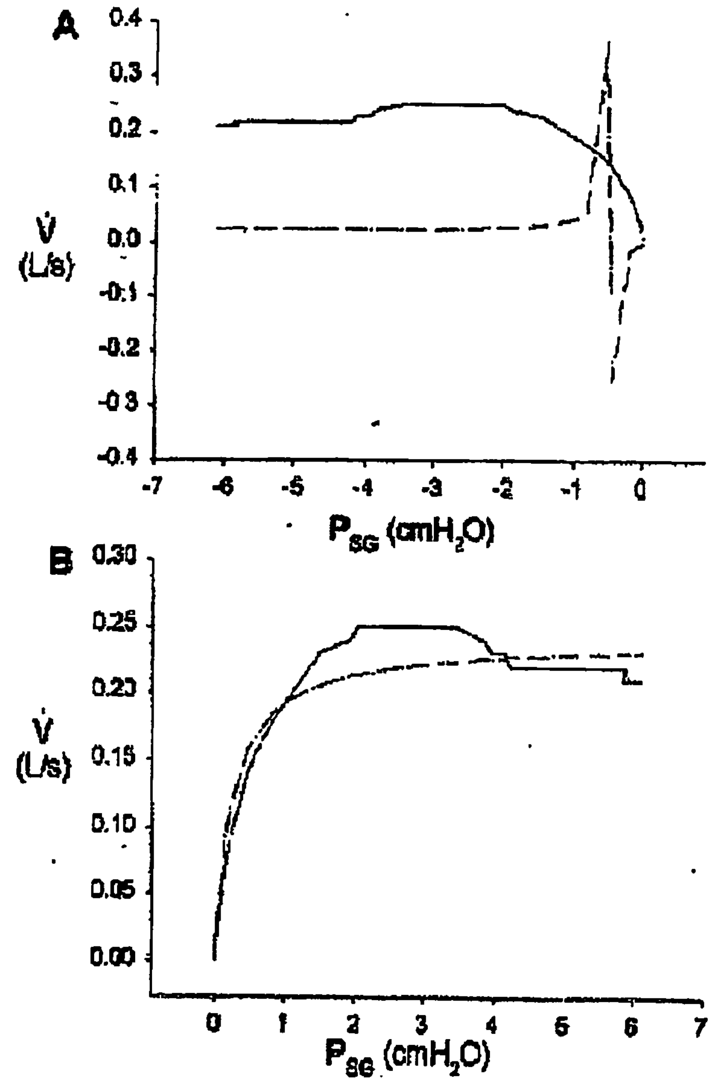


Figure 5

[redacted]

Figure 6


A
0.4
0.3
0.2
0.1
0.0
-0.1
-0.2
-0.3
-0.4
V̇ (L/s)
-7 -6 -5 -4 -3 -2 -1 0
P_SG (cmH2O)
B
0.30
0.25
0.20
0.15
0.10
0.05
0.00
V̇ (L/s)
0 1 2 3 4 5 6 7
P_SG (cmH2O)

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BIOMECHANICS OF SLEEP_RELATED UPPER AIRWAY OBSTRUCTION

by

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DISSERTATION

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Advisor	Date

CHAPTER 3

THEORY AND METHODS FOR DETERMINING INSPIRATORY FLOW LIMITATION AND RESISTANCE

Theory and Hypothetical Considerations

Determination of Flow Limitation

We consider a steady homogenous flow in a circular cylinder (the upper airway), with the assumption that the flow of air in the upper airway will expand without the loss or gain of heat. Consider a streamline of air, which connects two points M_1, the upstream pressure, which is atmospheric pressure in our model, and M_2, the downstream pressure, which is equivalent to supraglottic pressure in our model. For each point, there is a density (ρ), pressure (P), area (A), velocity (V) and flow (F) that characterize that point. In the modeling that follows, it should be noted that the goal is determination of the flow of the upper airway at the downstream pressure point, M_2. Flow, which is constant throughout the upper airway, is given by:

Total Energy= Kinetic Energy [T] + Potential Energy [E] + Internal Energy (1)

Internal energy =0

Differentiate both sides of equation (1)

$$dK = dT + dE \qquad (2)$$

$$T = \frac{1}{2}mV^2,\ E = pv \qquad (3)$$

The gas unit mass (m) is defined according equation (4)

$$m = \rho v = 1,\ v = \frac{1}{\rho},\ dv = d\left(\frac{1}{\rho}\right) \qquad (4)$$

$$dK = VdV + Pdv \qquad (5)$$

$$\frac{1}{2}V^2 + \int_{P_0}^{P_{\infty}} Pd\left(\frac{1}{\rho}\right) = const \qquad (6)$$

Integrating by part the second term

$$\frac{1}{2}V^2+\frac{P}{\rho_0}-\frac{P}{\rho_0}-\int_{\rho_0}^{\rho}\frac{dP}{\rho}=const \quad (7)$$

Since the path is short then $\rho_2 \cong \rho_1 = \rho$ (8a)

Rearrange and substitute $P = K\rho^{\gamma}$ (a), $dP = K\gamma\rho^{\gamma-1}$ (8b)

Substitute (8b) in (7)

We get

$$\frac{1}{2}V^2+\frac{P}{\rho}-\frac{P}{\rho_0}-\left(\frac{1}{\gamma-1}\right)\left[\frac{K\rho_0^{\gamma}}{\rho_0}-\frac{K\rho^{\gamma}}{\rho}\right]=const \quad (9)$$

The terms in equation (9) can be reduced as

$$\frac{P}{\rho_0}\cong\frac{P}{\rho} \text{ and } \frac{K\rho_0^{\gamma}}{\rho_0}=const$$

Continuity equation $P = \rho_1 A_1 V_1 = \rho_2 A_2 V_2$ (10)

Solving for V_1: $V_1 = \frac{\rho_2 A_2}{\rho_1 A_1}V_2 = \Omega V_2$ (11)

Where $\Omega = \frac{\rho_2 A_2}{\rho_1 A_1} = \frac{A_2}{A_1}$ (12)

The Bernoulli or energy equation for homogenous fluid such as air [91], on one streamline, through M_1, M_2 and neglecting the effect of gravity is:

$$\frac{P_1}{\rho_1}+\frac{1}{2}V_1^2=\frac{P_2}{\rho_2}+\frac{1}{2}V_2^2 \quad (13)$$

Because air is a compressible, we need to consider the heat kinematic ratio $\frac{\gamma}{\gamma-1}$. If we set the kinematic heat ratio as: $K=\frac{\gamma}{\gamma-1}$, then we can rewrite equation (13) as derived by equation (9) as:

$$K\frac{P_1}{\rho_1}+\frac{1}{2}V_1^2=K\frac{P_2}{\rho_2}+\frac{1}{2}V_2^2 \quad (14)$$

Because the path of the upper airway is short then we may assume $\rho_1 \cong \rho_2 = \rho$.

We can then rearrange equation 4 as:

$$P_1-P_2=\frac{\rho}{2K}\left(V_2^2-V_1^2\right) \quad (15)$$

Substituting V_1^2 from equation 2:

$$P_1-P_2=\frac{\rho}{2K}\left(V_2^2-\Omega^2V_2^2\right) \quad (16)$$

Solving for V_2^2:

$$V_2^2=2K\frac{\left(P_1-P_2\right)}{\rho\left(1-\Omega^2\right)} \quad (17)$$

Squaring both sides of equation 1, we can obtain the flow squared at point M_2:

$$F^2=\rho^2A_2^2V_2^2 \quad (18)$$

Substituting for V_2^2 from equation 7:

$$F^2=\frac{2\rho A_2^2K}{\left(1-\Omega^2\right)}\left(P_1-P_2\right) \quad (19)$$

Rearranging:

$$F^2=\frac{2\rho A_2^2K}{\left(1-\Omega^2\right)}P_1\left(1-\frac{P_2}{P_1}\right) \quad (20)$$

Taking the square root of both sides of equation 10, then we obtain

$$F = \left(\frac{2\rho A_2^2 K P_1}{(1-\Omega^2)}\right)^{\frac{1}{2}} \left(1 - \frac{P_2}{P_1}\right)^{\frac{1}{2}} \quad (21)$$

Let $G = \left(\frac{2\rho A_2^2 K P_1}{(1-\Omega^2)}\right)^{\frac{1}{2}}$

Therefore, flow through a streamline between two points, M_1 and M_2, is given by:

$$F = G\left(1 - \frac{P_2}{P_1}\right)^{\frac{1}{2}} \quad (22)$$

Using Newton's expansion law:

$$(1+X)^N = 1 + NX + \frac{N(N-1)}{2!}X^2 + \frac{N(N-1)(N-2)}{3!}X^3 + \dots$$

We obtain:

$$F = G + \frac{G}{2P_1}P_2 + \frac{G}{8P_1^2}P_2^2 + \frac{3G}{48P_1^3}P_2^3 + \dots \quad (23)$$

If we let, $A = \frac{3G}{48P_1^3}, B = \frac{G}{8P_1^2}, C = \frac{G}{2P_1}, D = G$

We can then substituting these coefficients into equation 23 to get a polynomial function that approximates flow (F) in terms of the supraglottic pressure. For this function, we assume that P_1 is atmospheric pressure, which is a constant, and P_2 = P, which we now define as the supraglottic pressure:

$$F = AP^3 + BP^2 + CP + D \quad (24)$$

Per Newton's expansion law, the relationship between pressure and flow could also be predicted by a quadratic equation:

$$F = AP^2 + BP + C \quad (25).$$

However, the nature of a polynomial function predicts that a polynomial function would be expected to better estimate the pressure-flow relationship than the quadratic function for flow-limited breaths. This is because for IFL breaths, the polynomial function is characterized by two deflections, as illustrated in Figure 8. A two deflection relationship will better approximate the measured pressure-flow relationship of IFL breaths, which are characterized by a point of maximum flow, followed by a decrease and plateau in flow (Figure 8). The quadratic function, however, is characterized by only one deflection (Figure 8), and therefore, does not as closely approximate the measured pressure-flow relationship of IFL breaths.

While performing the initial curve-fitting analysis (see Methods below), we noted that the nature of the polynomial function, in contrast to the quadratic function, would allow for the objective differentiation of IFL and NIFL breaths. In particular, we noted that for the polynomial function, the maximal flow of the predicted relationship usually was at same point as the measured maximal flow. In contrast, the predicted maximal flow for the quadratic function would be at a more negative pressure. To objectify these observations, we hypothesized that we could determine the presence of flow-limitation by examining derivative of the polynomial function, which is represented by the slope of the pressure-flow relationship. The derivative of the polynomial function is:

$$\frac{dF}{dP} = 3AP^2 + 2BP + C \quad (25)$$

Theoretically, for non-flow limited breaths, flow would continue to increase beyond the point of maximal flow if there were further decreases in supraglottic

pressure. Therefore, the derivative of the polynomial function (or the slope of the pressure-flow curve) at the actual maximal flow is negative. This is illustrated in Figure 9, (upper left panel), which shows a NIFL breath and the theoretic relationship using the polynomial function. At the measured maximal flow, the slope of the theoretic pressure-flow relationship is negative, as illustrated. However, for breaths that demonstrate inspiratory flow limitation, there are no further increases in flow despite decreasing supraglottic pressure. Therefore, the slope or derivative of the polynomial function at the measured maximal flow is either zero or positive for flow-limited breaths. This is also illustrated in Figure 9, (upper right panel). Therefore, at maximal flow, two cases can be determined from equation 25. If 1) $\frac{dF}{dP} < 0$, the breath is nonflow-limited; and 2) $\frac{dF}{dP} > 0$ or $\frac{dF}{dP} = 0$, the breath is flow-limited.

By a similar analysis we hypothesized that the derivative of the quadratic function cannot be used to determine if the pressure-flow relationship demonstrates flow limitation. The derivative of the quadratic function is given as:

$$\frac{dF}{dP} = 2AP + B \quad (26)$$

However, if the quadratic function is used to characterize the pressure-flow relationship, the derivative of the quadratic function cannot be used to distinguish between non-flow limited and flow-limited breaths. This is illustrated in the Figure 9 (lower panels), which shows that the derivative of the quadratic equation will be negative for both types of breaths. In other words, $\frac{dF}{dP} < 0$ for all breaths.

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In summary, theoretical considerations indicate that the relationship between flow and supraglottic pressure in the upper airway can be characterized by either a quadratic or polynomial function. However, based upon the theoretical considerations, we hypothesized that the polynomial function was the better of the two functions to mathematically model the upper airway because it would provide the best fit compared to the actual pressure-flow relationship and used its derivative would provide an objective and accurate method for the detection of inspiratory flow limitation.

<u>Linear resistance determination</u>

Usually as flow proceed from an area of high pressure to an area of low-pressure velocity of the air will increases, then the flow will change from laminar to turbulent. This is consistent with Bernoulli principle as reported by White [88]. In laminar the relation between pressure, and flow is linear and the turbulent flow then relatively non-linear [91].

In order to solve for the linear resistance, we are going to determine the flow in the laminar region, according to the following principle for viscous flow:

$F \propto P^{N}$, where F is the flow, P is the pressure, and N is an exponent. If N >1, or N<1 then the flow is turbulent. If N= 1 then the flow is laminar [85, 91].

Based on our relationship of equation $F(P) = AP^3 + BP^2 + CP - D$ this equation has two phases of flow, which are laminar and turbulent. Analyses should be carried out as follows

$$F(P) = AP^3 + BP^2 + CP + D = F_1 + F_2$$

Where $F_1 = AP^3 + BP^2$ for turbulent flow; $F_2 = CP - D$ for laminar flow. Therefore, we hypothesize that the reciprocal slope of the laminar flow is the first linear resistance: $R = \frac{1}{C} = \frac{\Delta P}{\Delta F}$.

Methods

Methods and data analyses for the data analyses were performed in several steps. In Protocol #1, Step #1 is the curve fitting of the actual data using 5 different functions. In Step #2, we will choose the functions that have the highest correlation R^2, and perform error fit method to select the functions with the least error fit. In Protocol #2, Step #1, we will apply the analytical theory to characterize the flow in 50 development breathes. In Step #4, we will characterize 544 breaths and perform sensitivity analyses to determine if the final function can determine the presence of IFL. In Protocol, #3, we will determine the linear resistance on the same 544 breaths and compare the results to manually measured resistance.

Measurements and manual determination of flow limitation

For each breath, airflow (V) was measured by a pneumotachometer (Model 3700A, Hans Rudolph Inc.) attached to a nasal mask. Supraglottic airway pressures were measured using a pressure-tipped catheter (Model TC-500XG, Millar Co.) threaded though the mask and positioned in the oropharynx just below the base of the tongue. Correct placement was verified by visually inspecting the catheter's position in the oropharynx

The sequences of the analysis is illustrated in figure 10. During the studies, airflow and supraglottic pressure were recorded simultaneously with

Biobench data acquisition software (National Instruments, Austin, TX) on a separate computer (figure 7, panel A). For each breath, the onset of inspiration was defined as the sampling point at which $V_I = 0$. On the rare occurrence in which there was a shift in baseline, the nadir flow was determined and the flow values shifted appropriately. Because the Millar catheter provides relative pressures, P_{SG} was set to zero for the inspiration onset sampling point and the remaining values for the breath were calculated. A pressure flow loop was generated and the loop was analyzed for the presence of inspiratory flow limitation (IFL) (Figure 7). A breath was labeled IFL if there was a 1 cmH_2O or greater decrease in supraglottic pressure without any corresponding increase in flow during inspiration. If the flow-pressure relationship did not meet this criterion, the breath was labeled as non-flow limited (NIFL).

All analyzed breaths in the following protocols were obtained during Stage 2 NREM sleep. Breaths from wakefulness were not analyzed, as IFL is not observed during wakefulness. As slow wave and REM sleep are uncommonly observed in the heavily instrumented subjects, breaths from these stages could not be analyzed. In addition, only breaths free from artifact were included in the analysis. All breaths were obtained from healthy noncomplaining adults who had volunteered for research studies in the laboratory. All subjects were free of sleep-disordered breathing, as measured by apneas and hypopneas on baseline polysomnography. Demographics of the subjects are presented within each protocol.

Protocol #1: Does the polynomial function best predict the relationship between pressure and flow in the upper airway?

Step 1: Curve Fitting: To model the upper airway mathematically, we performed a curve fitting analysis using Sigma Stat 2.0 software. The purpose of this analysis was to determine which of five regression equations (Table 1) best estimated inspiratory flow (the dependent variable) as a function of supraglottic pressure (the independent variable). This process is similar to performing a linear regression, in which the predicted relationship can be given by the equation: F (P) = AP + B. However, since the pressure-flow relationship is not linear, we used 5 non-linear regression functions. The first two are derived from the theoretical considerations above: quadratic and polynomial (Figure 11, left panel). The third, a single-term hyperbolic, has previously been proposed as an accurate predictor of the pressure-flow relationship (11). In addition, we analyzed 2 additional functions: double-term hyperbolic and exponential [44]. Neither the pressure nor flow values were transformed prior to the curve fitting [50]. This analysis was performed on 20 breaths, 10 NIFL, 10 IFL derived from 4 subjects (1 male, 3 females, mean age 22 ± 3 yrs, mean BMI 23.0 ± 3.0 kg/m^2). For each calculated function, we determined the coefficient of determination (R^2), which indicates how much of the variability in one variable (flow) is explained by knowing the value of the other (supraglottic pressure) (12). The R^2 for IFL and NIFL breaths were compared between the five functions using one-way repeated measures analysis of variance (ANOVA), with breath number as the repeated measure and the function as the factor for comparison. If there was a significant

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difference between the groups, a Student-Newman-Keuls test was performed to detect between group differences with $p<0.05$ set as the level for a significant test. The same test was performed on the combined groups of breaths.

<u>Step -2: Error Fit:</u> To determine the degree of approximation between the pressure-flow relationship derived from either the quadratic or polynomial function to the actual pressure-flow relationship, we determined the error-fit for 50 breaths, 25 each NIFL and IFL derived from 8 subjects (5 males, 3 females, mean age 25 ± 4 yrs, mean BMI 26.2 ± 4.8 kg/m²). Only the quadratic and polynomial functions were studied based upon the results of the curve fitting analysis (see Results, Chapter 4). An illustration of the concept of error-fit is given in Figure 11, right panel. The right panel shows the actual pressure-flow relationship for an IFL breath (solid line) and the predicted pressure-flow relationship using either the quadratic function (dashed line). The gray-shaded areas show the difference between the two relationships. The smaller the gray-shaded area, the smaller the error-fit and the more closely the predicted relationship approximates the actual pressure-flow relationship. The error-fit is a mathematical representation of this gray-shaded area. Mathematically, error fit is defined as:

$$100(\sum_i^k 1-(y_k - y_i)) \quad (18)$$

Where $\sum_i^k$ is the summation of a series of points, y_k represents the points in the original function and y_i represents the points in the fitted function [50]. Using this

formula, as the predicted pressure-flow relationship more closely approximates the actual relationship, the error-fit or difference between the two relationships decreases. The error-fit for IFL and NIFL breaths were compared between the five functions using one-way repeated measures analysis of variance (ANOVA), with breath number as the repeated measure and the function as the factor for comparison. If there was a significant difference between the groups, a Student-Newman-Keuls test was performed to detect between group differences with $p<0.05$ set as the level for a significant test. The same test was performed on the combined groups of breaths.

Protocol #2: Does the polynomial function objectively detect flow limitation?

Step 1: Using the same 50 breaths on which we determined the error-fit, we determined the slope at the measured maximal flow for the polynomial equation. Per theory, if the slope at the measured maximal flow was <0, we labeled the breath NIFL; if the slope at the measured maximal flow was ≥ 0, we labeled the breath IFL. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) for the detection of IFL breaths by the polynomial model compared to the standard method (described at the beginning of the Methods section) using standard formulas [63].

To confirm the theory that the slope at the measured maximal flow for the quadratic equation would be negative for both IFL and NIFL breaths, we determined the slope at the measured maximal flow for the same 50 breaths. We report the proportion of NIFL and IFL breaths with a negative slope.

<u>Step 2</u>: To validate the results, we then determined the slope at the measured maximal flow using the polynomial equation for 544 randomly selected breaths from 20 subjects without sleep-disordered breathing as measured by apneas and hypopneas (10 males, 10 females, mean age 30 ± 8 yrs. mean BMI 25.2 ± 4.3 kg/m²). Applying the hypothesis, we labeled each breath as NIFL or IFL. We calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value for the detection of IFL breaths by the polynomial model compared to the standard method using standard formulas [63].

<u>Protocol 3: Measurement of linear resistance</u>

Manual measurement for the resistance was done on the linear portion of the pressure- flow inspiratory cycle as it is shown in Figure 12 We draw a straight line from the origin of the axis and delineated the line through the rising edge of the inspiratory cycle. Then we calculate the slope of the line as $\frac{\Delta P}{\Delta F}$, where ΔP is the difference between two points on the pressure-axis, and ΔF are the difference between two points on the flow (F) axis. Calculated measurement of resistance was performed using the equation: $R_{UA} = 1/C$, where C is the coefficient from the curve fit polynomial equation. We compared the calculated resistance of the upper airway (cR_{UA}) to the measured upper airway resistance (mR_{UA}) in 544 breaths (same breaths as Protocol #2, Step #2) using Bland-Altman plots [96].

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